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Synthesis of 2'-aminoalkyl-1-benzylisoquinoline derivatives and medium sized ring analogues with mu opiod receptor binding activities.

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Abstract:

Novel 2'-aminoalkyl-1-benzylisoquinoline compounds and medium size ring analogues have been prepared using reductive alkylation methods. Four of these analogues were tested for biological activity across 48 different CNS receptors and were showed to have binding activities at the mu opiod receptor.

1. Introduction.

The 1-benzylisoquinolines alkaloids constitute a group of natural products of diverse structure that are widely present in many plants and mammalian species.^{1,2} About 2500 1-benzylisoquinoline alkaloids have been identified and shown to have a wide range of biological activities including anticancer,² antimalarial,³ anti-HIV,⁴ antiplatelet and vaso-relaxant.^{5,6} Several natural and synthetic benzylisoquinoline derivatives have also displayed affinities for dopamine and seretonin receptors, which are important neurotransmitters in the central nervous system (CNS).⁷ Examples of some of these 1-benzylisoquinoline derivatives are shown in Figure 1. Compounds with these biological activities have potential application in the treatment of numerous physiological and behavioural disorders such as schizophrenia, anxiety, Parkinson's and Huntington's disease.⁷

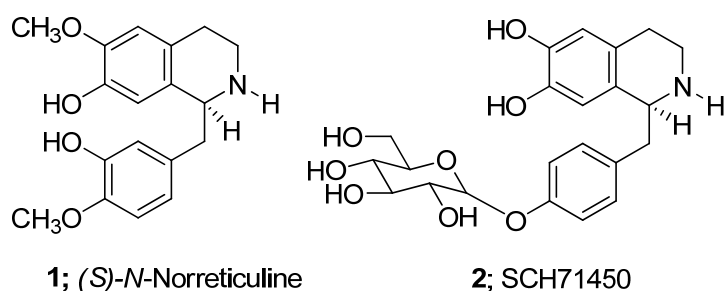


Figure 1. 1-Benzylisoquinoline derivatives that were found to be dopaminergic ligands in the micromolar range.⁷

There are also an emerging class of CNS active compounds that contain an amino group appended to a heterocyclic base structure (Figure 2), for example the high affinity 5HT_{1A} receptor agonist repinotan **3**⁸ and the 5HT₇ active molecule SB-691673 **4**.⁹ Medium sized ring CNS active compounds are known, including the D1-antagonist LE 300 **5**¹⁰ and the partial D1/D5 agonist SCH 39166 **6**.¹⁰⁻¹²

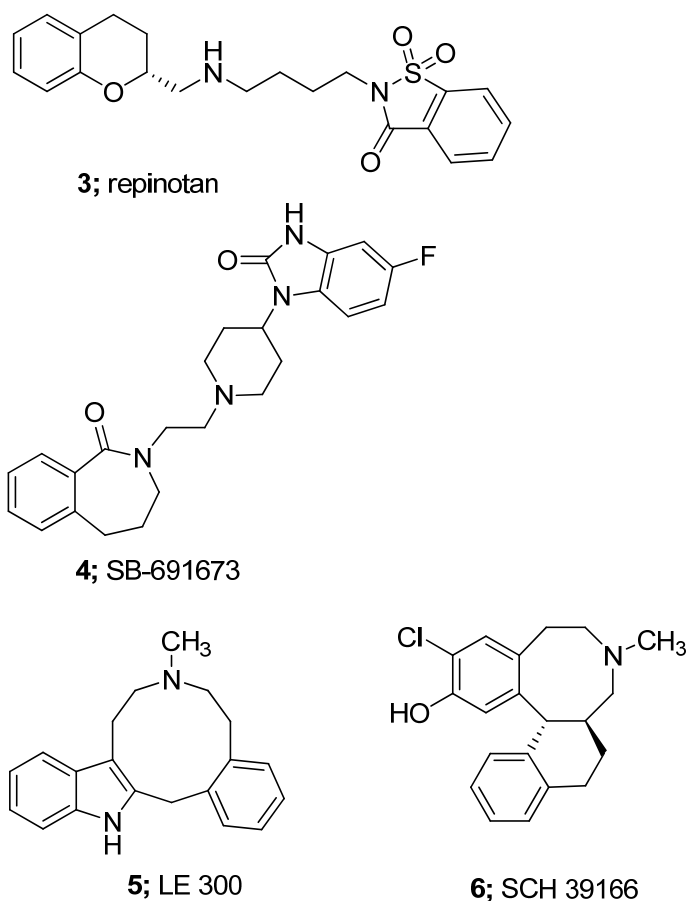


Figure 2. The structures of known CNS active compounds.⁸⁻¹²

In our continuing project concerned with the discovery of new bioactive benzyloisoquinoline derivatives,¹³⁻¹⁵ the 2'-aminoalkyl-1-benzyloisoquinoline compound **7** and the medium side ring analogues **8** were of interest. We report here our attempts to synthesise these compounds and the biological activities of four of these analogues on 48 different CNS receptors.

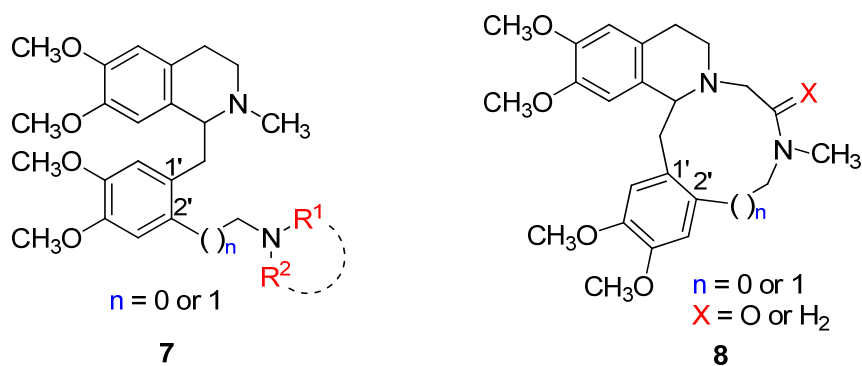
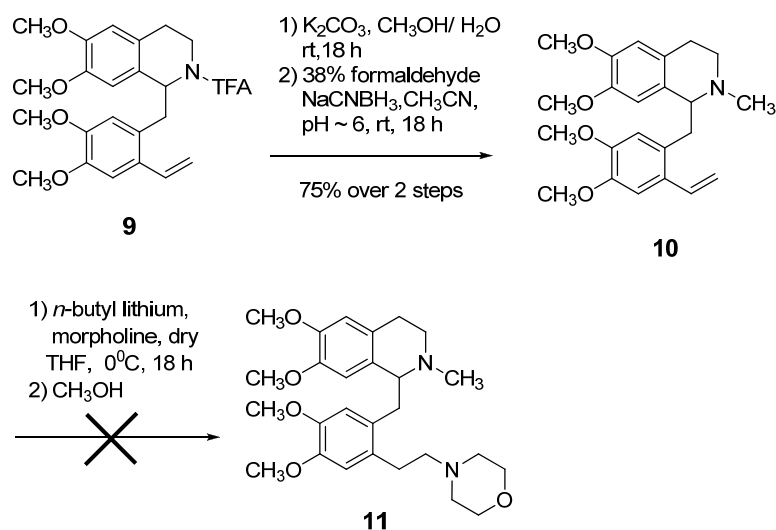


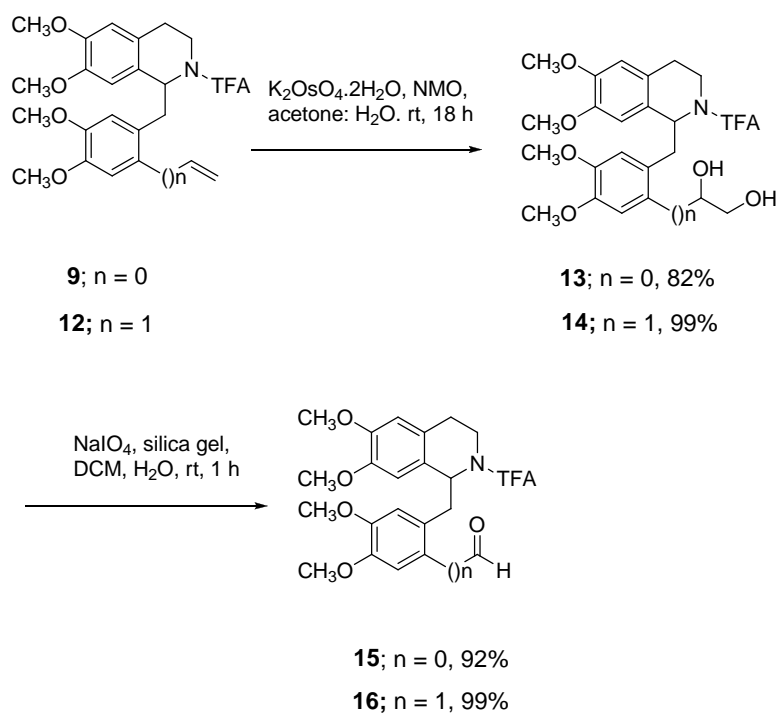
Figure 3. The targeted 1-benzyloisoquinoline derivatives containing 2'-aminoalkyl substituents (**7**) and the medium sized ring targets (**8**).

2. Results and Discussion.



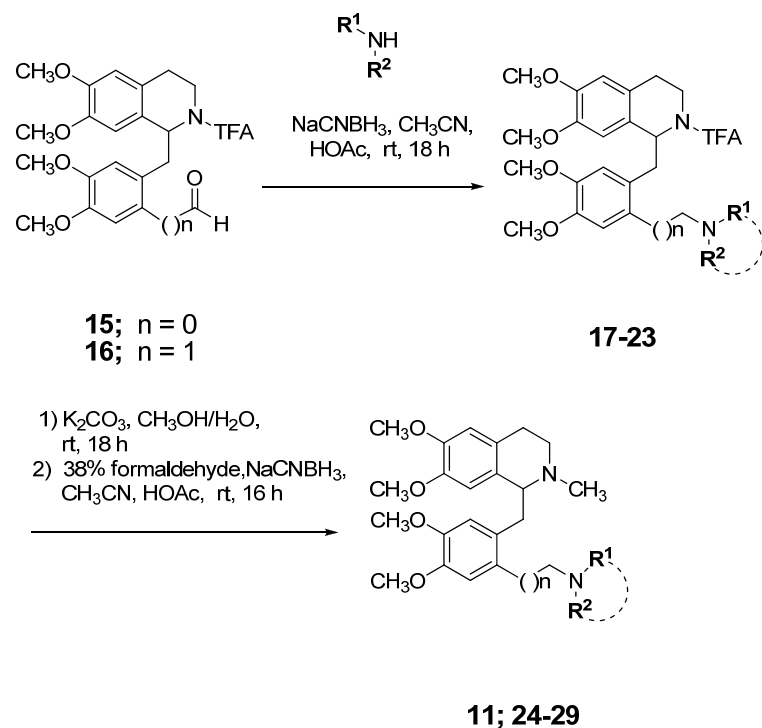
Scheme 1. Attempted synthesis of **11** using lithium morpholinamide and the 2'-vinylaudanosine derivative **10**.

With the aim of preparing 2'-aminoethyl-1-benzylisoquinoline derivatives, we first examined the method reported by Seijas *et al.* towards the preparation of β -phenylethylamines derivatives by addition of primary and secondary lithium amides to styrene.¹⁶ The racemic 2'-vinylaudanosine derivative **10** was prepared from the known *N*-TFA derivative **9**^{14,15} in 75% overall yield. Morpholine was treated with *n*-butyl lithium and the resulting solution of lithium morpholinamide in THF was added to compound **10** at 0 °C. The mixture was left at 0 °C for 18 h. ¹H NMR analysis only showed unreacted starting material **10** and no morpholine ethylene signals were observed. This suggests that the vinyl group of **10** was too electron rich to react with the lithium morpholinamide nucleophile. Therefore an alternative synthesis of the 2'-aminoethyl-1-benzylisoquinoline and 2'-aminomethyl-1-benzylisoquinoline derivatives was examined using a reductive amination method (Scheme 2). Here the racemic aldehydes **15** and **16** were prepared in good yields from the known alkenes **9** and **12**,¹⁴⁻¹⁵ respectively, using the 2 step sequence of dihydroxylation, followed by oxidative cleavage.^{17,18}



Scheme 2. Preparation of the aldehydes **15** and **16** *via* oxidative cleavage of the diols **13** and **14**, respectively.

The aldehydes **15** and **16** were subjected to reductive amination reactions with several amines to give the corresponding aminated products in moderate to good yields (Scheme 3, Table 1).



Scheme 3

Entry	Aldehyde	Amine		Reductive amination		N-TFA cleavage and N-methylation	
		R ¹	R ²	product	yield	product	yield
1	15	-CH ₂ CH ₂ -O-CH ₂ CH ₂ -		17	60%	24	73%
2	15	-CH ₂ CH ₂ CH ₂ CH ₂ -		18	74%	25	71%
3	15	CH ₂ CH ₃	CH ₂ CH ₃	19	75%	26	58%
4	15	H	CH(CH ₃) ₂	20	64%	27 (R ¹ = CH ₃)	59%
5	16	-CH ₂ CH ₂ -O-CH ₂ CH ₂ -		21	64%	11	85%
6	16	-CH ₂ CH ₂ CH ₂ CH ₂ -		22	74%	28	69%
7	16	CH ₂ CH ₃	CH ₂ CH ₃	23	68%	29	69%

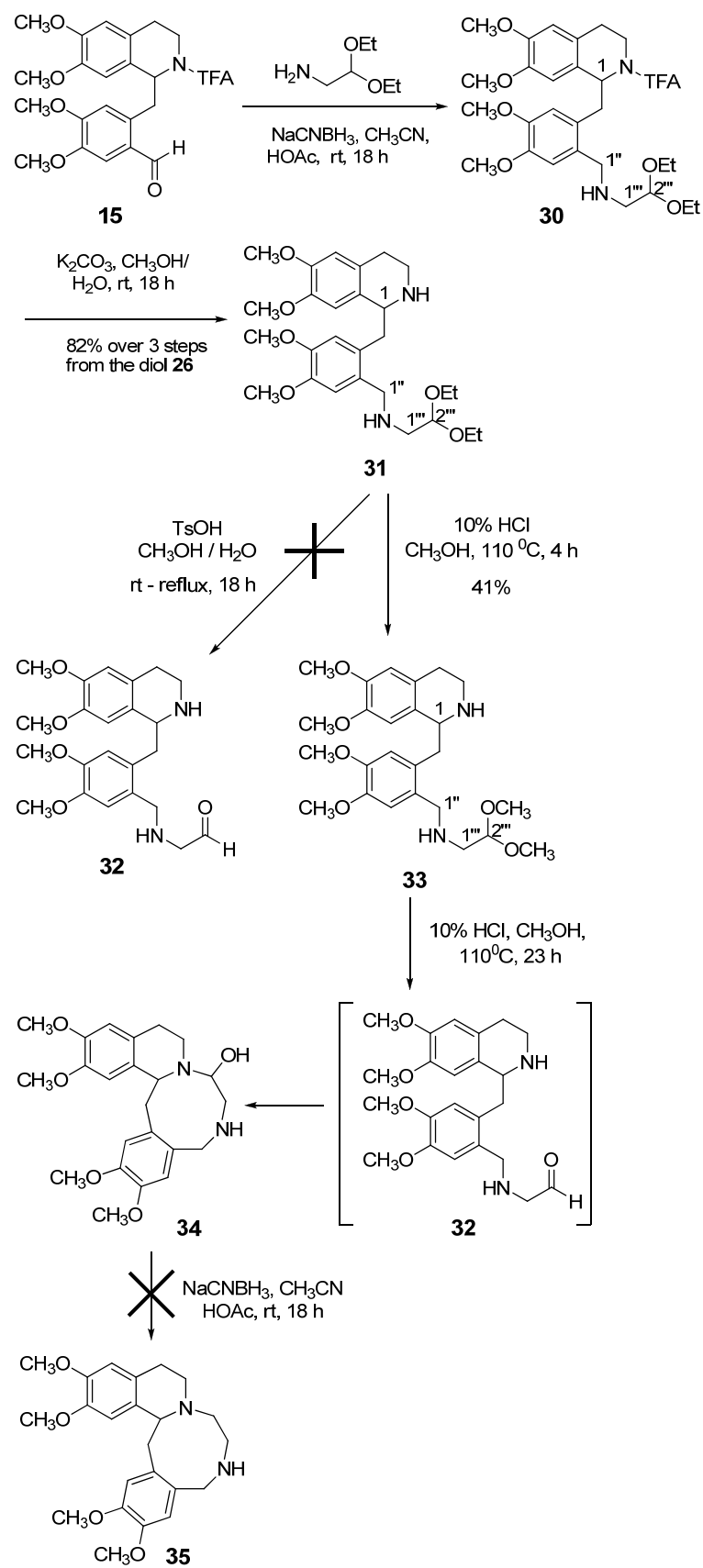
Table 1 Synthesis of 2'-aminomethyl-1-benzylisoquinoline analogues by reductive amination, followed by N-TFA cleavage and N-methylation.

The final 2'-aminoalkyl-1-benzylisoquinoline derivatives required for biological testing were obtained by basic hydrolysis of the TFA group of **17-23**, followed by reductive N-methylation using a literature procedure.¹⁹ The final products **11** and **24-29** were obtained in moderate to high yields (Table 1).

Overall, the above reductive amination procedure was an effective method used to synthesise a small library of seven 2'-aminoalkyl-1-benzylisoquinoline derivatives which represent a new class of 1-benzylisoquinolines.

The synthesis of the medium sized ring 1-benzylisoquinoline derivative **35** was attempted utilising the reductive amination method developed in Scheme 3 to facilitate the intramolecular coupling between the aldehyde and the amine group of **32** to provide the medium ring compound **35** (Scheme 4). The synthesis started with the reductive amination reaction between the aldehyde **15** and commercially available aminoacetaldehyde diethylacetal, followed by basic hydrolysis of the N-TFA group to afford the desired product **31** in 82% overall yield. Conversion of the diethoxyl acetal group of the bis-amine **31** into the corresponding aldehyde **32** was attempted using TsOH/CH₃OH/H₂O at rt to reflux temperature, however no product was obtained. Alternatively, the amine **31** was heated in a solution of 10% aqueous HCl/MeOH at

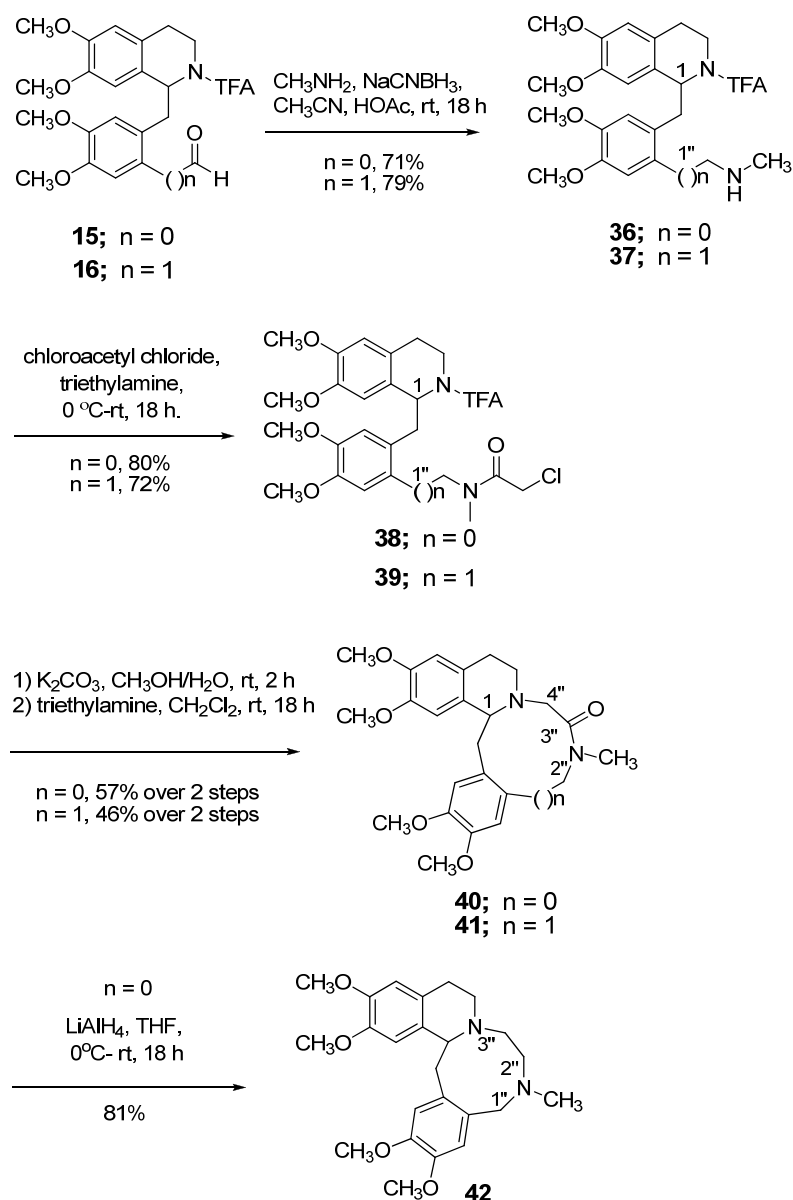
110 °C to afford only the corresponding dimethoxyl acetyl compound **33** which arose from exchange of the diethoxyl acetal group with the solvent methanol. Further heating of compound **33** in 10% aqueous HCl/MeOH afforded a crude product, which when ^1H NMR analysis was performed, showed that the dimethoxy signal at δ 3.36 (s, 6H, $\text{CH}(\text{OCH}_3)_2$) had disappeared, however, the expected aldehyde signal in the δ 9-10 region was not observed. ESIMS analysis showed a MH^+ signal at m/z 415.0 which would correspond to the hemiacetal **34**. The crude compound was subjected to the reductive amination conditions with NaCNBH_3 , however no identifiable products were obtained.



Scheme 4

Alternatively (Scheme 5), the aldehydes **15** and **16** were reductively coupled with methylamine to afford the corresponding benzyloquinolines **36** and **37** in 71% and 79% yield, respectively. The amines **36** and **37** subsequently underwent *N*-acylation with chloroacetyl chloride to give the corresponding α -chloroacetamides **38** and **39** in good yields (72-80%). Hydrolysis of the *N*-TFA group of **38** and **39** exposed the free amino groups for an intramolecular S_N2 displacement of the chloride under basic conditions with triethylamine to provide the desired medium ring compounds **40** and **41** in moderate yields (46-57% over 2 steps). The 9-membered ring **40** was subjected to carbonyl reduction using lithium aluminium hydride to afford the corresponding cyclic amino compound **42** in 81% yield. Analysis of the ¹H NMR spectrum of **42** revealed the newly formed methylene proton resonances for H2'' at δ 2.79 (m, 1H), 2.57 (m, 1H) and for H3'' at δ 3.10 (m, 1H), 2.79 (m, 1H). These newly observed methylene proton signals confirmed the successful amide reduction to the amine **42**. The benzylic protons of **42** were observed more prominently at δ 4.49 (d, 1H, *J* 12.5 Hz, H1'') and 3.42 (d, 1H, *J* 12.5 Hz, H1'').

o



Scheme 5

3. *In vitro* CNS Receptor Binding Studies.

The *in vitro* testing was conducted at Cerep Corporation in France. Four 2'-aminoalkyl-1-benzylisoquinoline derivatives **11**, **25**, **26** and **27** were tested for biological activities on 48 different CNS receptors.²⁰ The activities were expressed as % inhibition of control specific binding (Table 2), which is the measure of the direct inhibition activity of the tested drug exerted on the controlled ligand. Therefore the drug is considered active when the % inhibition of control specific binding is high at the CNS receptor type tested.

The CNS binding activities of the four derivatives **11**, **25-27** are shown in Table 2. All four compounds showed binding activities at the mu (μ) opiod receptor (MOP), with compound **11** having the highest mu receptor activity with 46% inhibition of the control (DAMGO) specific binding at 1 μ M concentration. Compound **26** was tested at 10 μ M concentration and was shown to have binding activities against several receptors, most prominently at the mu and kappa opiod (KOP) receptors, with inhibition activities of 52% and 40%, respectively. The IC₅₀ of these compounds are yet to be determined, but that of compound **11** and **27** would be estimated to be in the low micromolar range activities against the mu receptor.

Table 2

In vitro CNS receptor binding activities of compounds **11** and **25-27**. Across the 48 CNS receptors, only the receptors with 25 % or more of inhibition activities are illustrated below.

Assay	Reference compounds		% Inhibition of control specific binding at 1 μ M			
	Reference compound	IC ₅₀ (nM)	Compound 11	Compound 25	Compound 26 ^a	Compound 27
μ (h) (MOP)	DAMGO	1.2	46	25	52	35
κ (KOP)	U 50488	1.2	-	-	40	-
V _{1a} (h)	[d(CH ₂) ⁵ 1,Tyr(Me) ₂]-AVP	1.8	-	-	37	-
α_1 (non selective)	prazosin	0.30	-	-	25	-
Na ⁺ channel	veratridine	4650	-	-	25	-

^a Testing was conducted at 10 μ M concentration.

The symbol – indicate binding inhibition of less than 25 %.

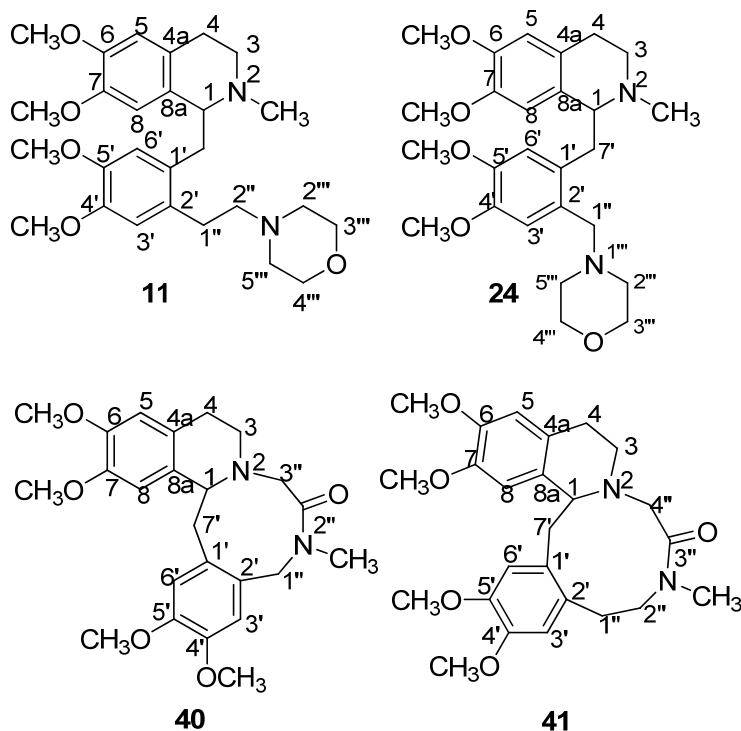
The mu opiod receptor is one major class of opiod receptors which has been targeted for its analgesic properties.²¹ Opiod agonists such as morphine exert their activities mainly at the mu opiod receptor and have been widely used in pain therapy.²¹ Chronic morphine therapy, however, can produce unwanted side effects such as tolerance,

respiratory suppression and constipation.²¹ Mu opioid antagonists are commonly used as a rescue medication to reverse these side effects as well as combating alcohol and narcotic addiction.²²⁻²³ Mu opioid antagonists also have potential applications in the treatment of obesity, psychosis and Parkinson's disease.²² Therefore, depending on their agonist or antagonist properties, compounds **11** and **25-27** and their analogues could be used in pain treatment therapy, or for the treatment of narcotic addictions as well as obesity, psychosis and Parkinson's disease.

In conclusion, seven novel 2'-aminoalkyl-1-benzylisoquinoline analogues and three medium sized ring 1-benzylisoquinoline analogues were successfully synthesised. Four analogues **11**, **25**, **26** and **27** showed moderate to good inhibition of control specific binding activities at 1-10 μ M concentrations against the mu receptor. Unfortunately, compounds **24**, **28-29** and **40-42** were unable to be tested.

4. Experimental

Petrol refers to the fraction of petroleum spirit with a boiling point of 40-60°C. All ¹H NMR spectra were performed at 300 MHz and all ¹³C NMR and DEPT spectra at 75 MHz in CDCl₃ solution, unless otherwise noted. All spectra were referenced to CDCl₃ (¹H δ 7.26 ppm and ¹³C NMR δ 77.00 ppm). ¹H NMR assignments were achieved with the aid of gCOSY, and in some cases NOESY and TOCSY experiments. ¹³C NMR assignments were based on DEPT, gHSQC and gHMBC experiments. All compounds were homogeneous by TLC analysis and judged to be of >95% purity based upon ¹H NMR analysis. Compound numbering of 1-benzylisoquinoline derivatives is based on that of compounds **11** and **24**. Compound numbering of the medium ring benzylisoquinoline derivatives is based on that of compounds **40** and **41**.



(*RS*) 1-(2'-Ethenyl-4',5'-dimethoxyphenyl)methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (10).

To a solution of the 2'-vinyllaudanosine derivative **9** (227 mg, 0.487 mmol) in a mixture of CH₃OH (20 mL) and H₂O (3 mL) at rt was added K₂CO₃ (339 mg, 2.44 mmol). The reaction mixture was stirred for 18 h at rt. The CH₃OH was evaporated and the residue was dissolved in CH₃CN (10 mL). 38% Formaldehyde (8 mL) was added to the solution, followed by NaCNBH₃ (41 mg, 0.633 mmol). The reaction was stirred for 20 min at rt and the pH was adjusted to ~6 using glacial acetic acid. The reaction mixture was stirred for 18 h at rt. The solvent was evaporated and the residue was dissolved in CH₂Cl₂ and washed with 1M aqueous NaOH, H₂O (2 x) and dried (K₂CO₃) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (3:7:0.1)) to give **10** (140 mg, 75% overall) as a yellow oil. *R*_f 0.25 (CH₃OH/EtOAc (1:1)). ¹H NMR: δ 6.97 (s, 1H, H3'), 6.73 (dd, 1H, *J* 17.4, 10.8 Hz, H1''), 6.54 (s, 1H, H5), 6.39 (s, 1H, H6'), 5.72 (s, 1H, H8), 5.45 (dd, 1H, *J* 17.4, 1.2 Hz, H2''(*E*)), 5.11 (dd, 1H, *J* 10.8, 1.2 Hz, H2''(*Z*)), 3.86 (s, 3H, OCH₃-4'), 3.80 (s, 3H, OCH₃-6), 3.72 (s, 3H, OCH₃-7), 3.68-3.62 (m, 1H, H1), 3.43 (s, 3H, OCH₃-5'), 3.28-3.25 (m, 1H, H3), 3.24 (dd, 1H, *J* 13.5, 4.8 Hz, H7'), 2.94-2.78 (m, 2H, H3, H4), 2.76 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.64-2.57 (m, 1H, H4), 2.54 (s, 3H, NCH₃). MS

(ESI⁺): *m/z* 384 (MH⁺, 20%). HRMS (ESI⁺): calcd for C₂₃H₃₀NO₄, 384.2175 (MH⁺), found 384.2180.

Attempted synthesis of (*RS*) 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(2''-morpholinoethyl)phenyl)methyl-2-methylisoquinoline (11).

To a solution of **10** (139.5 mg, 0.364 mmol) in dry THF (4 mL) was added a solution of lithium morpholinamide, prepared by the addition of 2.5M *n*BuLi in hexane (0.2 mL, 0.5 mmol) to a solution of morpholine (79.3 mg, 0.91 mmol, 0.1 mL) in dry THF (1 mL) at 0°C. The reaction mixture was kept at 0°C for 18 h. The reaction mixture as quenched with CH₃OH and the solvent was evaporated. The residue was purified by column chromatography to retrieve only a quantitative amount of starting material **10**.

General method for dihydroxylation.^{17,18}

To a solution of the olefin in acetone was added potassium osmate dihydrate (K₂OsO₄·2H₂O), followed by *N*-methylmorpholine *N*-oxide (NMO). H₂O was subsequently added and the mixture was stirred at rt for 18 h. Sodium sulfite (Na₂SO₃) (ca. 10 equiv.) was added and stirred for 30 min before the acetone was evaporated. Water was added and the mixture was extracted with CH₂Cl₂. The combined CH₂Cl₂ extracts were washed with brine, dried (MgSO₄), and evaporated to give an oil. The oil was purified by column chromatography (EtOAc) to afford the desired product.

(1*RS*, 1''*RS*) and (1*RS*, 1''*SR*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-[2'-(1'',2''-dihydroxyethyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline (13).

A solution of the olefin **9** (135 mg, 0.290 mmol) in acetone (3 mL) was treated as described above in the general dihydroxylation reaction procedure using K₂OsO₄·2H₂O (6 mg, 0.015 mmol), NMO (72 mg, 0.609 mmol) and H₂O (1 mL). Purification by column chromatography gave the diol **13** (119 mg, 82%) as a light yellow oil. The diol **13** was obtained as a 4:1 mixture of diastereomers. *R_f*: 0.39 (EtOAc). ¹H NMR of the major diastereomer: δ 6.99 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.31 (s, 1H, H6'), 6.08 (s, 1H, H8), 5.48 (dd, 1H, *J* 8.2, 5.8 Hz, H1), 5.08 (dd, 1H, *J* 8.1, 4.2 Hz, H1''), 3.94 (dt, 1H, *J* 13.5, 3.6 Hz, H3), 3.85 (s, 3H, OCH₃-7), 3.84 (s, 3H,

OCH₃-5'), 3.78 (dt, 1H, *J* 12.6, 4.8 Hz, H3), 3.69 (s, 3H, OCH₃-4'), 3.68-3.60 (m, 2H, 2xH2''), 3.57 (s, 3H, OCH₃-6), 3.17 (dd, 1H, *J* 13.5, 5.8 Hz, H7'), 3.03 (dd, 1H, *J* 13.5, 8.2 Hz, H7'), 2.98-2.93 (m, 1H, H4), 2.84-2.76 (m, 1H, H4). ¹H NMR of the minor diastereomer (in part): δ 6.95 (s, 1H, H3'), 6.49 (s, 1H, H5), 6.23 (s, 1H, H6'), 5.59 (t, 1H, *J* 7.5 Hz, H1), 4.94 (dd, 1H, *J* 8.1, 4.2 Hz, H1''), 3.77 (s, 3H, OCH₃-7), 3.73-3.71 (m, 2H, 2H2''), 3.68 (s, 3H, OCH₃-4'), 3.28-3.23 (m, 1H, H7'). ¹³C NMR of the major diastereomer: δ 156.3 (q, *J* 36.1 Hz, COCF₃), 148.1 (C5', C7), 147.6 (C4'), 147.0 (C6), 131.8 (C1'), 126.2 (C2'), 125.9 (C4a), 124.6 (C8a), 118.2 (q, *J* 285.1, COCF₃), 114.2 (CH-6'), 111.4 (CH-8), 110.8 (CH-5), 109.6 (CH-3'), 70.7 (CH-1''), 67.3 (CH₂-2''), 55.7 (4 x OCH₃), 55.5 (CH-1), 40.6 (CH₂-3), 38.0 (CH₂-7'), 28.2 (CH₂-4). ¹³C NMR of the minor diastereomer (in part): δ 132.1 (C1'), 126.1 (C2'), 124.4 (C8a), 114.4 (CH-6'), 110.2 (CH-5'), 109.5 (CH-3'), 67.5 (CH₂-2''), 28.3 (CH₂-4). MS (EI⁺): *m/z* 499 (M⁺, 20 %). HRMS (ESI⁺): calcd for C₂₄H₂₈F₃NNaO₇, 522.1716 (M+Na⁺), found 522.1724.

(1*RS*, 2''*RS*) and (*R,S*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-[2'-(2'',3'''-dihydroxypropyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline (14).

A solution of the olefin **12** (120 mg, 0.255 mmol) in acetone (7 mL) was treated as described above in the general dihydroxylation reaction procedure using K₂OsO₄·2H₂O (6 mg, 0.015 mmol), followed by NMO (63 mg, 0.537 mmol) and H₂O (1 mL) except the reaction mixture stirred for 5 h at rt. The crude oil was purified by column chromatography (EtOAc) to give the diol **14** (130 mg, 99%) as clear oil. The diol **14** was obtained as a 60:40 mixture of diastereomers. *R_f*: 0.38 (EtOAc). ¹H NMR of the major diastereomer: δ 6.71 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.39 (s, 1H, H6'), 6.27 (s, 1H, H8), 5.47 (dd, 1H, *J* 5.4, 3.3 Hz, H1), 4.02 (dt, 1H, *J* 8.1, 3.0 Hz, H3), 3.97-3.91 (m, 1H, H2''), 3.84 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.81-3.78 (m, 1H, H3''), 3.75-3.70 (m, 1H, H3), 3.69 (s, 3H, OCH₃-4'), 3.58-3.54 (m, 1H, H3''), 3.52 (s, 3H, OCH₃-6), 3.13 (dd, 1H, *J* 8.1, 3.3 Hz, H7'), 3.02 (dd, 1H, *J* 8.1, 5.4 Hz, H7'), 2.94-2.89 (m, 1H, H1''), 2.88-2.85 (m, 1H, H4), 2.83-2.79 (m, 1H, H4), 2.68-2.62 (m, 1H, H1''). ¹H NMR of the minor diastereomer (in part): δ 6.70 (s, 1H, H3'), 6.44 (s, 1H, H6'), 6.01 (s, 1H, H8), 5.59 (dd, 1H, *J* 5.4, 3.3 Hz, H1), 3.88-3.84 (m, 1H, H2''), 3.74 (s, 3H, OCH₃-4'), 3.66 (s, 3H, OCH₃-6), 3.15 (dd, 1H, *J* 8.1, 3.3 Hz, H7'), 3.03 (dd, 1H, *J* 8.1, 5.4 Hz, H7'), 2.97-2.94 (m, 1H, H1''), 2.75-2.71 (m, 1H, H1''). ¹³C

NMR of the major diastereomer: (signals for COCF_3 and COCF_3 were not observed), δ 148.3 (C7), 148.2 (C5'), 147.5 (C6), 147.3 (C4'), 129.3 (C1'), 127.7 (C2'), 126.2 (C4a), 124.6 (C8a), 114.5 (CH-6'), 113.3 (CH-3'), 111.0 (CH-8, CH-5), 73.1 (CH-2''), 66.2 (CH₂-3''), 55.0 (4 x OCH₃), 55.7 (CH-1), 40.8 (CH₂-3), 38.6 (CH₂-7'), 35.7 (CH₂-1''), 28.5 (CH₂-4). ¹³C NMR of the minor diastereomer (in part): δ 148.3 (C7), 147.3 (C6), 148.0 (C5'), 147.1 (C4'), 129.0 (C1'), 127.9 (C2'), 126.6 (C4a), 124.8 (C8a), 114.0 (CH-6'), 113.1 (CH-3'), 110.9 (CH-5), 110.4 (CH-8), 72.9 (CH-2''), 66.0 (CH₂-3''), 55.6 (CH-1), 40.4 (CH₂-3), 38.5 (CH₂-7'), 36.0 (CH₂-1''), 28.6 (CH₂-4). MS (EI⁺): m/z 513 (M⁺, 20%). HRMS (ESI⁺): calcd for C₂₅H₃₁F₃NO₇, 514.2053 (MH⁺), found 514.2064.

General method for oxidative cleavage of diols.

To a warm solution (*ca* 40 °C) of NaIO₄ in H₂O was added silica gel with vigorous stirring. The powder was cooled and a solution of the diol in CH₂Cl₂ was added. The mixture was stirred vigorously for 1 h at rt. The CH₂Cl₂ layer was collected by pipetting and the silica was washed several times with CH₂Cl₂. The combined CH₂Cl₂ washings were evaporated to give pure aldehydes without the need for further purification.

(*RS*) 1-(2'-Formyl-4',5'-dimethoxyphenyl)methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (15)

Silica gel coated with NaIO₄ was prepared as above using NaIO₄ (827 mg, 3.89 mmol), H₂O (2 mL) and silica gel (1.7 g). To this powder was added a solution of the vicinal diol **14** (167 mg, 0.335 mmol) in CH₂Cl₂ (3 mL) which was treated as described above in the general oxidative cleavage reaction procedure to afford the pure aldehyde **15** (144 mg, 92%) as a white solid. R_f 0.80 (EtOAc). m.p. 154-158⁰C. ¹H NMR: δ 9.90 (bs, 1H, CHO), 7.28 (s, 1H, H3'), 6.74 (s, 1H, H5), 6.59 (s, 2H, H6', H8), 5.64 (dd, 1H, J 8.7, 5.7 Hz, H1), 3.92 (s, 3H, OCH₃-7), 3.88 (s, 3H, OCH₃-5'), 3.84 (s, 3H, OCH₃-4'), 3.79 (s, 3H, OCH₃-6), 3.71-3.54 (m, 3H, 2xH3, H7'), 3.15 (dd, 1H, J 13.5, 8.1 Hz, H7'), 2.94-2.88 (m, 1H, H4), 2.86-2.70 (m, 1H, H4). ¹³C NMR: (signals for COCF_3 and COCF_3 were not observed), δ 190.8 (CHO), 153.0 (C4'), 148.3 (C6), 148.0 (C5'), 147.8 (C7), 134.1 (C2'), 127.6 (C4a), 126.5 (C1'), 124.7 (C8a), 114.6 (CH-6'), 113.9 (CH-3'), 110.9 (CH-8), 110.3 (CH-5), 56.0 (OCH₃-7, OCH₃-5'), 55.9 (OCH₃-4', OCH₃-6), 55.1 (CH-1), 40.3 (CH₂-3), 37.7 (CH₂-7'), 28.6 (CH₂-4).

MS (EI⁺): m/z 467 (M⁺, 10%). HRMS (ESI⁺): calcd for C₂₃H₂₅F₃NO₆, 468.1634 (MH⁺), found 468.1642.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-oxoethyl)phenyl]methylisoquinoline (16).

Silica gel coated with NaIO₄ was prepared as above using NaIO₄ (676 mg, 3.18 mmol), H₂O (2 mL) and silica gel (1.7 g). To this solution was added a solution of diol **14** (134 mg, 0.265 mmol) in CH₂Cl₂ (3 ml) which was reacted as described above in the general oxidative cleavage reaction procedure to give the pure aldehyde **16** (127 mg, 99%) as a clear oil. Compound **16** was a 95:5 mixture of rotamers. *R_f*: 0.88 (EtOAc). ¹H NMR of the major rotamer: δ 9.61 (t, 1H, *J* 2.1 Hz, CHO), 6.60 (s, 2H, H3', H5), 6.50 (s, 1H, H6'), 6.02 (s, 1H, H8), 5.33 (dd, 1H, *J* 8.7, 5.4 Hz, H1), 3.90 (dt, 1H, *J* 12.6, 4.5 Hz, H3), 3.86 (s, 6H, OCH₃-7, OCH₃-5'), 3.74 (s, 3H, OCH₃-4'), 3.67 (dd, 1H, *J* 8.4, 3.6 Hz, H3), 3.55 (s, 3H, OCH₃-6), 3.55-3.47 (m, 2H, 2xH1"), 3.07 (dd, 1H, *J* 13.5, 5.4 Hz, H7'), 2.91 (dd, 1H, *J* 13.5, 8.9 Hz, H7'), 2.89-2.85 (m, 1H, H4), 2.83-2.78 (m, 1H, H4). ¹H NMR of the minor rotamer (in part): δ 9.43 (bs, CHO), 5.87 (s, 1H, H8). ¹³C NMR of the major rotamer: δ 199.6 (CHO), 156.1 (q, *J* 35.8 Hz, COCF₃), 148.3 (C4'), 148.2 (C6), 148.2 (C5'), 147.2 (C7), 128.4 (C2'), 125.9 (C4a), 124.9 (C1'), 123.4 (C8a), 116.5 (q, *J* 286.4 Hz, COCF₃), 114.5 (CH-6'), 113.9 (CH-3'), 110.9 (CH-8), 110.8 (CH-5), 56.0 (OCH₃-7), 55.9 (OCH₃-5', OCH₃-4'), 55.7 (OCH₃-6), 55.6 (CH-1), 47.8 (CH₂-1"), 40.8 (CH₂-3), 38.5 (CH₂-7'), 28.6 (CH₂-4). ¹³C NMR of the minor rotamer (in part): δ 199.0 (CHO), 40.9 (CH₂-3), 55.4 (CH-1), 47.9 (CH₂-1"). MS (EI⁺): m/z 481 (M⁺, 10%). HRMS (ESI⁺): calcd for C₂₄H₂₇F₃NO₆, 482.1790 (MH⁺), found 482.1812.

General method of reductive amination.

To a solution of the aldehyde and the amine in CH₃CN was added NaCNBH₃. The reaction was stirred at RT for 20 min before glacial acetic acid was added to adjust the pH to ~ 6. The resulting solution was stirred for 18 h at RT. The CH₃CN was evaporated and the residue was dissolved in CH₂Cl₂. The solution was washed subsequently with H₂O (3 x), sat. Na₂CO₃, brine and dried (MgSO₄) to give an oil. The oil was purified by column chromatography to afford the pure product.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(morpholino)methylphenyl]methylisoquinoline (17).

A mixture of the aldehyde **22** (58 mg, 0.125 mmol), morpholine (0.10 mL, 1.16 mmol), CH₃CN (15 mL) and NaCNBH₃ (10 mg, 0.162 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (EtOAc) to afford **28** (40 mg, 60%) as a clear oil. Compound **28** was a 95:5 mixture of rotamers. *R_f*: 0.38 (EtOAc). ¹H NMR of the major rotamer: δ 6.73 (s, 1H, H3'), 6.59 (s, 1H, H5), 6.47 (s, 1H, H6'), 6.24 (s, 1H, H8), 5.78 (t, 1H, *J* 7.2 Hz, H1), 4.04-3.95 (m, 1H, H3), 3.83 (s, 6H, OCH₃-7, OCH₃-5'), 3.75 (dt, 1H, *J* 7.8, 6.7 Hz, H3), 3.74 (s, 3H, OCH₃-4'), 3.65 (t, 4H, *J* 4.8 Hz, 2xH3'', 2xH4''), 3.61 (s, 3H, OCH₃-6), 3.41 (d, 1H, *J* 12.9 Hz, H1''), 3.22 (dd, 1H, *J* 13.5, 7.2 Hz, H7'), 3.19 (d, 1H, *J* 12.9 Hz, H1''), 3.08 (dd, 1H, *J* 13.5, 7.2 Hz, H7'), 3.00-2.90 (m, 1H, H4), 2.81-2.73 (m, 1H, H4), 2.44-2.39 (m, 4H, 2xH2'', 2xH5''). ¹H NMR of the minor rotamer (in part): δ 6.71 (s, 1H, H3'), 6.50 (s, 1H, H6'), 5.96 (s, 1H, H8). ¹³C NMR of the major rotamer: (signals for C=O and C=O were not observed), δ 148.2 (C4'), 147.9 (C6), 147.4 (C5', C7), 128.9 (C2'), 128.7 (C8a), 127.2 (C1'), 124.8 (C4a), 114.2 (CH-3'), 114.1 (CH-6'), 111.0 (CH-5), 110.4 (CH-8), 67.0 (CH₂-3'', CH₂-4''), 61.4 (CH₂-2'', CH₂-5''), 55.9 (OCH₃-7, OCH₃-5'), 55.8 (OCH₃-4'), 55.7 (OCH₃-6), 55.0 (CH-1), 53.7 (CH₂-1''), 40.1 (CH₂-3), 37.9 (CH₂-7'), 28.7 (CH₂-4). MS (EI⁺): *m/z* 538 (M⁺, 30%). HRMS (ESI⁺): calcd for C₂₇H₃₄F₃N₂O₆, 539.2369 (MH⁺), found 539.2363.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(pyrrolidinyl)methylphenyl]methylisoquinoline (18).

A mixture of the aldehyde **15** (91 mg, 0.194 mmol), pyrrolidine (0.10 mL, 1.13 mmol), CH₃CN (3 mL) and NaCNBH₃ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc (4:6)) to afford **18** (77 mg, 74%) as a light yellow oil. Compound **18** was a 95:5 mixture of rotamers. *R_f*: 0.20 (CH₃OH/EtOAc (4: 6)). ¹H NMR of the major rotamer: δ 6.97 (s, 1H, H3'), 6.59 (s, 1H, H5), 6.34 (s, 1H, H6'), 6.04 (s, 1H, H8), 5.44 (dd, 1H, *J* 8.1, 6.1 Hz, H1), 3.93-

3.87 (m, 1H, H3), 3.87 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.80-3.75 (m, 1H, H3), 3.69 (s, 3H, OCH₃-4'), 3.56 (s, 3H, OCH₃-6), 3.42 (d, 1H, *J* 6.6 Hz, H1''), 3.38 (d, 1H, *J* 6.6 Hz, H1''), 3.16 (dd, 1H, 13.5, *J* 6.1 Hz, H7'), 3.08 (dd, 1H, *J* 13.5, 8.1 Hz, H7'), 2.97-2.87 (m, 1H, H4), 2.83-2.74 (m, 5H, H4, H2''', 2xH5'''), 1.92-1.84 (m, 4H, 2xH3''', 2xH4'''). ¹H NMR minor rotamer (in part): δ 6.79 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.44 (s, 1H, H6'), 6.04 (s, 1H, H8). ¹³C NMR of the major rotamer: (signals for COCF₃ and COCF₃ were not observed), δ 148.3 (C4', C6), 148.1 (C5'), 147.2 (C7), 128.3 (C2'), 126.9 (C1'), 126.2 (C4a), 125.1 (C8a), 114.4 (CH-6'), 113.5 (CH-3'), 111.0 (CH-5), 110.7 (CH-8), 56.5 (CH₂-1''), 56.2 (OCH₃-7), 56.0 (OCH₃-5'), 55.8 (OCH₃-4', OCH₃-6), 55.7 (CH-1), 53.6 (CH₂-2''', CH₂-5'''), 40.8 (CH₂-3), 38.4 (CH₂-7'), 28.5 (CH₂-4), 23.3 (CH₂-3''', CH₂-4'''). MS (EI⁺): *m/z* 522 (M⁺, 20%). HRMS (ESI⁺): calcd for C₂₇H₃₄F₃N₂O₅, 523.2420 (MH⁺), found 523.2435.

(*R,S*) 1-[2'-(Diethylamino)methyl-4',5'-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-dihydro.-6,7-dimethoxyisoquinoline (19).

A mixture of aldehyde **15** (112 mg, 0.239 mmol), diethylamine (0.2 mL, 1.93 mmol), CH₃CN (3 mL) and NaCNBH₃ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc (4:6)) to afford **19** (83 mg, 75%) as a light yellow oil. Compound **19** was a 95:5 mixture of rotamers. *R_f*: 0.33 (CH₃OH:EtOAc (4:6)). ¹H NMR of the major rotamer: δ 6.85 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.56 (s, 1H, H6'), 6.12 (s, 1H, H8), 5.55 (t, 1H, *J* 7.8, 6.0 Hz, H1), 3.92 (dt, 1H, *J* 7.8, 3.3 Hz, H3), 3.82 (s, 6H, OCH₃-7, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.73-3.66 (m, 1H, H3), 3.57 (s, 3H, OCH₃-6), 3.32 (dd, 1H, *J* 13.5, 7.8 Hz, H7'), 3.28 (d, 1H, *J* 13.5 Hz, H1''), 3.16 (d, 1H, *J* 13.5 Hz, H1''), 3.04 (dd, 1H, *J* 13.5, 6.0 Hz, H7'), 2.98-2.85 (m, 1H, H4), 2.77-2.69 (m, 1H, H4), 2.43 (q, 4H, *J* 6.9 Hz, 2 x NCH₂CH₃), 0.93 (t, 6H, *J* 6.9 Hz, 2 x NCH₂CH₃). ¹H NMR of the minor rotamer (in part): δ 6.79 (s, 1H, H3'), 5.85 (s, 1H, H8), 3.79 (s, 6H, OCH₃-7, OCH₃-5'), 3.48 (s, 3H, OCH₃-6). ¹³C NMR of the major rotamer: (signals for COCF₃ and COCF₃ were not observed), δ 148.4 (C4'), 147.7 (C6), 147.7 (C5'), 147.5 (C7), 128.5 (C2', C8a), 127.2 (C1'), 125.0 (C4a), 114.0 (CH-3'), 113.6 (CH-6'), 111.2 (CH-5), 110.7 (CH-8), 55.2 (OCH₃-7), 56.1 (OCH₃-5'), 55.1 (OCH₃-4'), 55.9 (OCH₃-6), 55.7 (CH-1), 55.5 (CH₂-1''), 46.5 (2

x NCH₂CH₃), 40.6 (CH₂-3), 37.7 (CH₂-7'), 28.8 (CH₂-4), 11.5 (2 x NCH₂CH₃). MS (EI⁺): *m/z* 524 (M⁺, 10%). HRMS (ESI⁺): calcd for C₂₇H₃₅F₃N₂O₅, 525.2576 (MH⁺), found 525.2563.

(*R,S*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(isopropylamino)methylphenyl]methylisoquinoline (20).

A mixture of aldehyde **15** (112 mg, 0.239 mmol), isopropylamine (0.2 mL, 2.33 mmol), CH₃CN (3 mL) and NaCNBH₃ (16 mg, 0.252 mmol) was reacted as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc (4:6)) to afford **20** (67 mg, 64%) as a light yellow oil. Compound **20** was a 95:5 mixture of rotamers. *R_f*: 0.17 (CH₃OH/EtOAc (4:6)). ¹H NMR of the major rotamer: δ 6.80 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.54 (s, 1H, H6'), 6.12 (s, 1H, H8), 5.58 (t, 1H, *J* 8.1, 6.6 Hz, H1), 3.95-3.85 (m, 1H, H3), 3.83 (s, 3H, OCH₃-7), 3.81 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.71-3.65 (m, 1H, H3), 3.56 (s, 3H, OCH₃-6), 3.48 (d, 1H, *J* 12.6 Hz, H1''), 3.43 (d, 1H, *J* 12.6 Hz, H1''), 3.20 (dd, 1H, *J* 13.8, 8.1 Hz, H7'), 3.05 (dd, 1H, *J* 13.8, 6.6 Hz, H7'), 2.96-2.85 (m, 1H, H4), 2.82-2.70 (m, 2H, H2'', H4), 1.04 (d, 3H, *J* 2.4 Hz, CH(CH₃)CH₃), 1.02 (d, 3H, *J* 2.4 Hz, CH(CH₃)CH₃). ¹H NMR of the minor rotamer (in part): δ 6.76 (s, 1H, H3'), 5.92 (s, 1H, H8), 3.77 (s, 3H, OCH₃-5'), 3.49 (s, 3H, OCH₃-6). ¹³C NMR of the major rotamer: (signals for C=O and C=O were not observed), δ 148.4 (C4'), 148.0 (C6), 147.9 (C5'), 147.5 (C7), 131.9 (C2'), 127.9 (C8a), 126.9 (C1'), 125.1 (C4a), 114.1 (CH-3'), 113.1 (CH-6'), 111.2 (CH-5), 110.7 (CH-8), 56.0 (OCH₃-7), 56.1 (OCH₃-5'), 55.1 (OCH₃-4'), 55.9 (OCH₃-6), 55.8 (CH-1), 49.3 (CH₂-1''), 49.2 (CH-2''), 40.7 (CH₂-3), 38.0 (CH₂-7'), 28.8 (CH₂-4), 23.1 (CH(CH₃)CH₃), 22.1 (CH(CH₃)CH₃). MS (EI⁺): *m/z* 510 (M⁺, 10%). HRMS (ESI⁺): calcd for C₂₆H₃₄F₃N₂O₅, 511.2421 (MH⁺), found 511.2395.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(morpholino)ethyl)phenyl]methylisoquinoline (21).

A mixture of aldehyde **16** (80 mg, 0.166 mmol), morpholine (0.1 mL, 1.16 mmol), CH₃CN (6 mL), NaCNBH₃ (16 mg, 0.252 mmol) was treated as described above in

the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc (4:6)) to afford **21** (59 mg, 64%) as a clear oil. Compound **21** was a 95:5 mixture of rotamers. *R_f*: 0.25 (CH₃OH/EtOAc (4:6)). ¹H NMR of the major rotamer: δ 6.66 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.52 (s, 1H, H6'), 6.01 (s, 1H, H8), 5.48 (t, 1H, *J* 6.9 Hz, H1), 3.92 (dt, 1H, *J* 13.5, 5.1 Hz, H3), 3.81 (s, 6H, OCH₃-7, OCH₃-5'), 3.72 (s, 3H, OCH₃-4'), 3.67 (t, 4H, *J* 4.7 Hz, 2xH3'', 2xH4''), 3.67-3.62 (m, 1H, H3), 3.53 (s, 3H, OCH₃-6), 3.05 (d, 2H, *J* 6.9 Hz, 2xH7'), 2.96-2.86 (m, 1H, H4), 2.78-2.70 (m, 1H, H4), 2.63-2.57 (m, 1H, H2''), 2.56-2.49 (m, 1H, H2''), 2.40 (t, 4H, *J* 4.7 Hz, 2xH2'', 2xH5''), 2.37-2.25 (m, 2H, 2xH1''). ¹H NMR of the minor rotamer (in part): δ 6.64 (s, 1H, H3'), 6.56 (s, 1H, H5), 5.75 (s, 1H, H8), 3.81 (s, 6H, OCH₃-7, OCH₃-5'), 3.77 (s, 3H, OCH₃-4'), 3.45 (s, 3H, OCH₃-6). ¹³C NMR of the major rotamer: δ 156.1 (q, *J* 35.3 Hz, C=OCF₃), 148.5 (C4'), 148.1 (C6), 147.5 (C5'), 147.4 (C7), 131.5 (C1'), 127.2 (C2'), 126.6 (C4a), 125.2 (C8a), 116.7 (q, *J* 286.5 Hz, COCF₃), 114.2 (CH-6'), 113.1 (CH-3'), 111.2 (CH-5), 110.9 (CH-8), 67.2 (CH₂-3'', CH₂-4''), 60.5 (CH₂-2''), 55.8 (4 x OCH₃), 55.7 (CH-1), 53.9 (CH₂-2'', CH₂-5''), 40.9 (CH₂-3), 38.2 (CH₂-7'), 29.7 (CH₂-1''), 28.7 (CH₂-4). ¹³C NMR of the minor rotamer (in part): δ 147.9 (C5'), 147.1 (C7), 131.8 (C1'), 127.0 (C2'), 126.0 (C4a), 111.2 (CH-5), 110.4 (CH-8), 65.9 (CH₂-3'', CH₂-4''), 60.1 (CH₂-2''), 53.8 (CH₂-2'', CH₂-5''), 40.9 (CH₂-3), 39.2 (CH₂-7'), 31.8 (CH₂-1''), 27.4 (CH₂-4). MS (ESI⁺): *m/z* 552.81 (MH⁺, 100%). HRMS (ESI⁺): calcd for C₂₈H₃₆F₃N₂O₆, 553.2525 (MH⁺), found 553.2486.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-Dimethoxy-2'-(2''-(*N*-pyrrolidinyl)ethyl)phenyl]methylisoquinoline (22**).**

A mixture of aldehyde **16** (71 mg, 0.149 mmol), pyrrolidine (0.2 mL, 2.26 mmol), CH₃CN (3 mL) and NaCNBH₃ (12 mg, 0.194 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH/ EtOAc (4:6)) to afford **22** (61 mg, 74%) as a light yellow oil. Compound **22** was a 95:5 mixture of rotamers. *R_f*: 0.20 (CH₃OH/EtOAc (4:6)). ¹H NMR of the major rotamer: δ 6.64 (s, 1H, H3'), 6.60 (s, 1H, H5), 6.56 (s, 1H, H6'), 6.02 (s, 1H, H8), 5.50 (dd, 1H, *J* 8.4, 5.7 Hz, H1), 3.93 (dt, 1H, *J* 13.8, 5.4 Hz, H3), 3.89 (s, 6H, OCH₃-7, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.71-

3.62 (m, 1H, H3), 3.53 (s, 3H, OCH₃-6), 3.05 (dd, 1H, *J* 13.5, 8.4 Hz, H7'), 3.02 (dd, 1H, *J* 13.5, 5.7 Hz, H7'), 2.96-2.81 (m, 1H, H4), 2.78-2.69 (m, 1H, H4), 2.58-2.35 (m, 8H, 2xH2'', 2xH5'', 2xH1'', 2xH2''), 1.80-1.76 (m, 4H, 2xH3'', 2xH4''). ¹H NMR of the minor rotamer (in part): 6.61 (s, 1H, H3'), 5.75 (s, 1H, H8), 3.39 (s, 3H, OCH₃-6). ¹³C NMR of the major rotamer: (signals for COCF₃ and COCF₃ were not observed), δ 148.2 (C4'), 148.8 (C6), 147.2 (C5', C7), 131.44 (C2'), 127.0 (C4a), 126.3 (C1'), 124.8 (C8a), 113.6 (CH-5), 111.7 (CH-3'), 110.9 (CH-6'), 110.4 (CH-8), 57.7 (CH₂-2''), 55.9 (OCH₃-7, OCH₃-5'), 55.6 (OCH₃-4', OCH₃-6, CH-1), 54.0 (CH₂-2'', CH₂-5''), 40.5 (CH₂-3), 37.8 (CH₂-7'), 31.9 (CH₂-1''), 28.5 (CH₂-4), 23.4 (CH₂-3'', CH₂-4''). MS (EI⁺): *m/z* 536 (M⁺, 10%). HRMS (ESI⁺): calcd for C₂₈H₃₆F₃N₂O₅, 537.2576 (MH⁺), found 537.2581.

(*RS*) 1-[2'-(2''-(Diethylamino)ethyl)-4',5'-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (23).

A mixture of aldehyde **16** (132 mg, 0.274 mmol), diethylamine (0.2 mL, 1.93 mmol), CH₃CN (3 mL) and NaCNBH₃ (22 mg, 0.356 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc (4:6)) to afford **23** (100 mg, 68%) as a light yellow oil. Compound **23** was a 95:5 mixture of rotamers. *R_f* 0.21 (CH₃OH/EtOAc (4:6)). ¹H NMR of the major rotamer: δ 6.63 (s, 1H, H3'), 6.57 (s, 2H, H5, H6'), 6.03 (s, 1H, H8), 5.49 (dd, 1H, *J* 8.4, 6.0 Hz, H1), 3.93 (dt, 1H, *J* 13.5, 5.7 Hz, H3), 3.82 (s, 3H, OCH₃-7), 3.82 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-4'), 3.71-3.64 (m, 1H, H3), 3.54 (s, 3H, OCH₃-6), 3.10 (dd, 1H, *J* 13.5, 8.4 Hz, H7'), 3.03 (dd, 1H, *J* 13.5, 6.0 Hz, H7'), 2.94-2.86 (m, 1H, H4), 2.79-2.71 (m, 1H, H4), 2.55 (q, 4H, *J* 6.9 Hz, 2 x NCH₂CH₃), 2.59-2.42 (m, 4H, 2xH1'', 2xH2''), 1.01 (t, 6H, *J* 6.9 Hz, 2 x NCH₂CH₃). ¹H NMR of the minor rotamer (in part): δ 6.60 (s, 1H, H3'), 3.52 (s, 3H, OCH₃-6). ¹³C NMR of the major rotamer: δ 155.6 (q, *J* 36.2 Hz, COCF₃), 148.2 (C4'), 147.89 (C6), 147.2 (C5', C7), 131.5 (C2'), 127.0 (C4a), 126.3 (C1'), 124.9 (C8a), 116.0 (q, *J* 286.3 Hz, COCF₃), 113.8 (CH-5), 112.8 (CH-3'), 110.9 (CH-6'), 110.5 (CH-8), 55.9 (OCH₃-7, OCH₃-5', CH-1), 54.6 (OCH₃-4', OCH₃-6), 54.2 (CH₂-2''), 46.6 (2 x NCH₂CH₃), 40.7 (CH₂-3), 38.0 (CH₂-7'), 29.6 (CH₂-1''), 28.5 (CH₂-4),

11.5 (2 x NCH₂CH₃). MS (EI⁺): *m/z* 538 (M⁺, 10%). HRMS (ESI⁺): calcd for C₂₈H₃₈N₂O₅F₃, 539.2733 (MH⁺), found 539.2734.

General method for *N*-Trifluoroacetyl deprotection and reductive *N*-Methylation.

The *N*-TFA protected amine was dissolved in a mixture of CH₃OH and H₂O. To this was added K₂CO₃ and the resulting solution was stirred at rt for 18 h. CH₃OH was removed and the residue was dissolved in CH₃CN. 38 % Formaldehyde was added followed by NaCNBH₃. Glacial acetic acid was added after 20 min of stirring to adjusted the pH to ~ 6. The reaction mixture was stirred at rt for 18 h. CH₃CN was evaporated and the residue was redissolved in CH₂Cl₂. The CH₂Cl₂ layer was washed with sat. K₂CO₃ and dried (MgSO₄). Evaporation of the CH₂Cl₂ extracts gave the crude product which was purified by column chromatography to afford the pure *N*-methylated analogues.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(morpholino)methyl phenyl]methyl-2-methylisoquinoline (24**).**

The *N*-TFA protected amine **17** (40 mg, 0.074 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (50 mg, 0.370 mmol), CH₃OH (5 mL) and H₂O (1 mL), except it was stirred at 80 °C for 3 h, then using 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (6 mg, 0.096 mmol) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (4:6:0.1)) to afford **24** (25 mg, 73%) as a clear oil. *R_f*: 0.34 (CH₃OH/EtOAc/NH₃ (4:6: 0.1)). ¹H NMR: δ 6.80 (s, 1H, H3'), 6.58 (s, 1H, H5), 5.41 (s, 1H, H6'), 5.71 (s, 1H, H8), 3.85 (s, 3H, OCH₃-7), 3.84 (s, 3H, OCH₃-5'), 3.81 (dd, 1H, *J* 9.0, 5.2 Hz, H1), 3.76 (s, 3H, OCH₃-4'), 3.66 (t, 4H, *J* 2.7 Hz, 2xH3'', 2xH4''), 3.44 (s, 3H, OCH₃-6), 3.29-3.25 (m, 1H, H3), 3.19 (d, 1H, *J* 12.9 Hz, H1''), 3.17 (dd, 1H, *J* 13.5, 5.2 Hz, H7'), 2.96 (dd, 1H, *J* 13.4, 9.0 Hz, H7'), 3.07 (d, 1H, *J* 12.9 Hz, H1''), 2.88-2.85 (m, 1H, H4), 2.81 (dt, 1H, *J* 9.3, 3.0 Hz, H3), 2.63 (dd, 1H, *J* 5.7, 3.0 Hz, H4), 2.56 (s, 3H, NCH₃), 2.36 (t, 4H, *J* 2.7 Hz, H2'', H5''). MS (ESI⁺): *m/z* 457.1 (MH⁺, 40%). HRMS (ESI⁺): calcd for C₂₇H₃₉N₂O₅, 471.2859 (MH⁺), found 471.2865.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy 1-[4',5'-dimethoxy-2'-(pyrrolidinyl)methyl phenyl]methyl-2-methylisoquinoline (25).

The *N*-TFA protected amine **18** (79 mg, 0.148 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reactions procedure by initially using K₂CO₃ (101 mg, 0.740 mmol), CH₃OH (5 mL) and H₂O (1 mL) and then 38 % formaldehyde (3mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (4:6:0.1)) to afford **25** (48 mg, 71% yield) as a light yellow oil. *R*_f 0.34 (CH₃OH/EtOAc/NH₃ (4:6:0.1)). ¹H NMR: δ 6.91(s, 1H, H3'), 6.55 (s, 1H, H5), 5.44 (s, 1H, H6'), 5.76 (s, 1H, H8), 3.85 (s, 3H, OCH₃-7), 3.81 (s, 3H, OCH₃-5'), 3.86-3.80 (m, 1H, H1), 3.72 (s, 3H, OCH₃-6), 3.49 (d, 1H, *J* 12.9 Hz, H1''), 3.44 (s, 3H, OCH₃-4'), 3.29 (d, 1H, *J* 12.9 Hz, H1''), 3.23-3.11 (m, 2H, H3, H7'), 2.94-2.78 (m, 3H, H7', H3, H4), 2.63-2.54 (m, 1H, H4), 2.52 (s, 3H, NCH₃), 2.41 (bs, 4H, 2xH2''', 2xH5'''), 1.70 (bs, 4H, 2xH3''', 2xH4'''). ¹³C NMR: δ 147.5 (C4', C6), 147.2 (C5'), 147.2 (C7), 130.8 (C2', C4a), 129.4 (C1'), 125.9 (C8a), 114.9 (CH-5), 113.4 (CH-3'), 111.8 (CH-6'), 111.5 (CH-8), 64.1 (CH-1), 57.8 (CH₂-1''), 56.3 (OCH₃-7), 56.1 (OCH₃-5', OCH₃-4'), 55.5 (OCH₃-6), 54.3 (CH₂-2''', CH₂-5'''), 46.3 (CH₂-3), 42.7 (NCH₃), 37.1 (CH₂-7'), 25.1 (CH₂-4), 23.8 (CH₂-3''', CH₂-4'''). MS (ESI⁺): *m/z* 441.1 (MH⁺, 100%). HRMS (ESI⁺): calcd for C₂₆H₃₆N₂O₄, 441.2753 (MH⁺), found 441.2777.

(*RS*) 1-[2'-(Diethylamino)methyl-4',5'-dimethoxyphenyl]methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (26).

The *N*-TFA protected amine **19** (75 mg, 0.161 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (109 mg, 0.810 mmol), CH₃OH (2 mL) and H₂O (1 mL), except it was stirred for 4 h and then using 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (4:6:0.1)) to afford **26** (41 mg, 58%) as a light yellow oil. *R*_f 0.32 (CH₃OH/EtOAc/NH₃ (4:6:0.1)). ¹H NMR: δ 6.88 (s, 1H, H3'), 6.54 (s, 1H, H5), 5.51 (s, 1H, H6'), 5.69 (s, 1H, H8), 3.83 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.74 (s, 3H, OCH₃-6), 3.70 (dd, 1H, *J* 9.0, 4.8 Hz, H1), 3.40 (s, 3H,

OCH₃-4'), 3.31-3.24 (m, 1H, H3), 3.18 (d, 1H, *J* 13.5 Hz, H1"), 3.08 (dd, 2H, *J* 13.5, 4.8 Hz, H7'), 2.98 (d, 1H, *J* 13.5 Hz, H1"), 2.89 (dd, 1H, *J* 9.6, 3.0 Hz, H3), 2.84 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.80-2.76 (m, 1H, H4), 2.60-2.56 (m, 1H, H4), 2.54 (s, 3H, NCH₃), 2.49-2.29 (m, 4H, 2 x NCH₂CH₃), 0.90 (t, 6H, *J* 6.9 Hz, 2 x NCH₂CH₃). ¹³C NMR: δ 147.3 (C4'), 147.2 (C6), 146.9 (C5'), 145.9 (C7), 131.1 (C2'), 130.7 (C4a), 128.9 (C1'), 125.6 (C8a), 114.8 (CH-5), 113.1 (CH-3'), 111.3 (CH-6'), 111.2 (CH-8), 64.1 (CH-1), 56.0 (CH₂-1"), 55.9 (OCH₃-7), 55.8 (OCH₃-5'), 55.3 (OCH₃-4'), 55.0 (OCH₃-6), 46.6 (2 x NCH₂CH₃), 46.0 (CH₂-3), 42.5 (NCH₃), 36.5 (CH₂-7'), 25.1 (CH₂-4), 11.6 (2 x NCH₂CH₃). MS (ESI⁺): *m/z* 443.2 (MH⁺, 100%). HRMS (ESI⁺) calcd for C₂₆H₃₉N₂O₄, 443.2910 (MH⁺), found 443.2928.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(isopropylamino)methyl)phenyl]methyl-2-methylisoquinoline (27).

The *N*-TFA protected amine **20** (60 mg, 0.136 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (91 mg, 0.680 mmol), CH₃OH (3 mL) and H₂O (1 mL), except it was stirred for 4 h, and then using 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (4:6:0.1)) to afford **27** (36 mg, 59%) as a light yellow oil. *R_f*: 0.34 (CH₃OH/EtOAc/NH₃ (4:6:0.1)). ¹H NMR: δ 6.82 (s, 1H, H3'), 6.54 (s, 1H, H5), 5.52 (s, 1H, H6'), 5.67 (s, 1H, H8), 3.82 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-6), 3.76-3.70 (m, 1H, H1), 3.39 (s, 3H, OCH₃-4'), 3.32-3.20 (m, 1H, H3), 3.12 (d, 1H, *J* 12.9 Hz, H1"), 2.95 (d, 1H, *J* 12.9 Hz, H1"), 2.96-2.77 (m, 5H, H4, 2xH7', H3, H2"), 2.61-2.52 (m, 1H, H4), 2.54 (s, 3H, NCH₃), 0.94 (t, 6H, *J* 2.1 Hz, CH(CH₃)CH₃). ¹³C NMR: δ 147.6 (C4'), 147.5 (C6), 147.2 (C5'), 146.0 (C7), 130.5 (C2', C4a), 128.0 (C1'), 125.1 (C8a), 114.3 (CH-5), 113.4 (CH-3'), 111.3 (CH-6'), 111.1 (CH-8), 64.2 (CH-1), 56.1 (OCH₃-7), 55.9 (OCH₃-5'), 55.8 (OCH₃-4'), 55.3 (OCH₃-6), 54.4 (CH₂-1"), 53.2 (CH-2'''), 45.9 (CH₂-3), 36.7 (CH₂-7'), 35.8 (NCH₃), 24.9 (CH₂-4), 17.7 (CH(CH₃)CH₃), 17.2 (CH(CH₃)CH₃). MS (ESI⁺): *m/z* 443.1 (MH⁺, 100%). HRMS (ESI⁺): calcd for C₂₆H₃₉N₂O₄, 443.2910 (MH⁺), found 443.2910.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''')-(morpholino)ethyl]phenyl)methyl-2-methylisoquinoline (1).

The *N*-TFA protected amine **21** (50 mg, 0.092 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (91 mg, 0.68 mmol), CH₃OH (3 mL) and H₂O (1 mL), then 38% formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (10 mg, 0.164 mmol) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (4:6:0.1)) to afford **11** (37 mg, 85%) as a light yellow oil. *R*_f 0.30 (CH₃OH/EtOAc/NH₃ (4 : 6 : 0.1)). ¹H NMR: δ 6.61 (s, 1H, H3'), 6.55 (s, 1H, H5), 6.53 (s, 1H, H6'), 5.68 (s, 1H, H8), 3.80 (s, 3H, OCH₃-7), 3.78 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-4'), 3.67 (t, 4H, *J* 4.5 Hz, 2H2'', 2H5''), 3.65-3.62 (m, 1H, H1), 3.38 (s, 3H, OCH₃-6), 3.28-3.20 (m, 1H, H3), 3.15 (dd, 1H, *J* 13.2, 4.2 Hz, H7'), 2.94-2.87 (m, 1H, H4), 2.85-2.81 (m, 1H, H3), 2.74 (dd, 1H, *J* 13.2, 9.6 Hz, H7'), 2.61-2.54 (m, 1H, H4), 2.53 (s, 3H, NCH₃), 2.38 (t, 4H, *J* 5.1 Hz, 2xH3'', 2xH4''), 2.34-2.27 (m, 2H, H2''), 2.24-2.17 (m, 2H, H1''). ¹³C NMR: δ 147.4 (C4'), 147.3 (C6), 147.1 (C5'), 146.0 (C7), 131.0 (C2'), 129.4 (C4a), 128.1 (C1'), 125.2 (C8a), 114.0 (CH-5), 112.8 (CH-3'), 111.2 (CH-6', CH-8), 66.8 (CH₂-3'', CH₂-4''), 64.3 (CH-1), 59.9 (CH₂-2''), 55.9 (OCH₃-7), 55.9 (OCH₃-5'), 55.7 (OCH₃-4'), 55.3 (OCH₃-6), 53.5 (CH₂-2'', CH₂-5''), 45.9 (CH₂-3), 42.2 (NCH₃), 37.1 (CH₂-7'), 29.5 (CH₂-1''), 24.7 (CH₂-4). MS (ESI⁺): *m/z* 471.1 (MH⁺, 40%). HRMS (ESI⁺): calcd for C₂₇H₃₉N₂O₅, 471.2859 (MH⁺), found 471.2865.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''')-(pyrolidino)ethyl] phenyl)methyl-2-methylisoquinoline (28).

The *N*-TFA protected amine **22** (38 mg, 0.076 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by using initially K₂CO₃ (52 mg, 0.381 mmol), CH₃OH (5 mL) and H₂O (1 mL), then 38% formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (10 mg, 0.164 mmol) to give an oil. The oil purified by column chromatography (CH₃OH/EtOAc/NH₃ (4:6:0.1)) to afford **28** (25 mg, 69%) as a light yellow oil. *R*_f 0.30 (CH₃OH/EtOAc/NH₃ (4:6:0.1)). ¹H NMR: δ 6.63 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.54

(s, 1H, H6'), 5.74 (s, 1H, H8), 3.81 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.66 (dd, 1H, *J* 9.0, 4.5 Hz, H1), 3.42 (s, 3H, OCH₃-6), 3.24 (m, 1H, H3), 3.09 (dd, 1H, *J* 13.5, 4.5 Hz, H7'), 2.94-2.87 (m, 1H, H4), 2.82-2.74 (m, 1H, H3), 2.78 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.61-2.58 (m, 1H, H4), 2.54 (s, 3H, NCH₃), 2.52-2.30 (m, 8H, 2xH1'', 2xH2'', 2xH2''', 2xH5'''), 1.75 (t, 4H, *J* 3.9 Hz, 2xH3''', 2xH4'''). ¹³C NMR: δ 149.4 (C4'), 148.9 (C6), 148.4 (C5'), 147.0 (C7), 128.4 (C2'), 126.3 (C4a), 121.5 (C1'), 120.2 (C8a), 115.0 (CH-5), 113.0 (CH-3'), 111.7 (CH-6'), 111.5 (CH-8), 65.2 (CH₂-2''), 56.4 (OCH₃-7, OCH₃-5'), 56.2 (OCH₃-4'), 55.6 (OCH₃-6), 53.3 (CH₂-1), 47.1 (CH₂-2''', CH₂-5'''), 45.3 (CH₂-3), 44.3 (NCH₃), 40.0 (CH₂-7'), 37.8 (CH₂-1''), 27.4 (CH₂-4), 21.4 (CH₂-3''', CH₂-4'''). MS (ESI⁺): *m/z* 454.92 (MH⁺, 20%). HRMS (ESI⁺): calcd for C₂₇H₃₉N₂O₄, 455.2910 (MH⁺), found 455.2907.

(*RS*) 1-[2'-(2'''-(Diethylamino)ethyl)-4',5'-dimethoxyphenyl]methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (29).

The *N*-TFA protected amine **23** (80 mg, 0.149 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (100 mg, 0.735 mmol), CH₃OH (5 mL) and H₂O (1 mL), then 38% formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (4:6:0.1)) to afford **29** (65 mg, 69%) as a light yellow oil. *R*_f 0.31 (CH₃OH/EtOAc/NH₃ (4:6:0.1)). ¹H NMR: δ 6.61 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.54 (s, 1H, H6'), 5.71 (s, 1H, H8), 3.81 (s, 3H, OCH₃-7), 3.79 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.66 (dd, 1H, *J* 9.0, 4.2 Hz, H1), 3.40 (s, 3H, OCH₃-6), 3.27-3.21 (m, 1H, H3), 3.09 (dd, 1H, *J* 13.0, 4.2 Hz, H7'), 2.92-2.86 (m, 1H, H4), 2.83-2.78 (m, 1H, H3), 2.78 (dd, 1H, *J* 13.0, 9.0 Hz, H7'), 2.59-2.54 (m, 1H, H4), 2.55 (s, 3H, NCH₃), 2.52 (q, 4H, *J* 4.2 Hz, 2 x NCH₂CH₃), 2.52-2.44 (m, 2H, 2xH2''), 2.35 (dt, 2H, *J* 12.3, 4.1 Hz, 2xH1''), 1.00 (t, 6H, *J* 4.2 Hz, 2 x NCH₂CH₃). ¹³C NMR: δ 148.2 (C4', C6), 148.0 (C5'), 146.5 (C7), 129.0 (C2', C4a), 125.9 (C1'), 124.8 (C8a), 114.0 (CH-5), 112.7 (CH-3'), 111.2 (CH-6'), 111.0 (CH-8), 64.5 (CH-1), 56.0 (OCH₃-7, OCH₃-5'), 55.7 (OCH₃-4', OCH₃-6), 55.2 (CH₂-2''), 45.9 (2 x NCH₂CH₃), 45.3 (CH₂-3), 41.2 (NCH₃), 36.8 (CH₂-7'), 27.3 (CH₂-1''), 23.4 (CH₂-4), 8.8 (2 x NCH₂CH₃). MS (ESI⁺):

m/z 456.94 (MH^+ , 30%). HRMS (ESI⁺): calcd for $C_{27}H_{41}N_2O_4$, 457.3066 (MH^+), found 457.3060.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1[2'-((2''',2'''-diethoxyethylamino)methy)-4',5'-dimethoxyphenyl]methylisoquinoline (31).

The aldehyde **15** was freshly generated from the diol **13** (139 mg, 0.278 mmol) as described in the general oxidative cleavage reaction procedure using a suspension of silica gel coated with $NaIO_4$, using $NaIO_4$ (827 mg, 3.89 mmol), H_2O (2 mL), silica gel (1.7 g) and CH_2Cl_2 (5 mL). To the solution of the aldehyde **15** in CH_3CN (4 mL) was added aminoacetaldehyde diethylacetal (487 mg, 3.67 mmol, 0.5 mL) and $NaCNBH_3$ (12 mg, 0.475 mmol). The reaction mixture was stirred at rt for 20 min and the pH was adjusted to ~ 6 using glacial acetic acid. The reaction mixture was stirred for 18 h at rt. The CH_3CN was evaporated and the residue was dissolved in a mixture of CH_3OH (10 mL) and H_2O (3 mL). K_2CO_3 (100 mg, 0.737 mmol) was added and the mixture was stirred at rt for 18 h. CH_3OH was evaporated and the residue was dissolved in CH_2Cl_2 . The solution was washed with H_2O (3x), brine and dried (K_2CO_3) to give an oil which was purified by column chromatography (EtOAc increase to $CH_3OH/EtOAc/NH_3$ (3:7:0.1)) to give **31** (118 mg, 82% over 3 steps) as a yellow oil. R_f 0.07 ($CH_3OH/EtOAc$ (5:5)). 1H NMR: (500 MHz) δ 6.84 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.60 (s, 1H, H6'), 6.54 (s, 1H, H8), 4.61 (t, 1H, J 5.0 Hz, H2'''), 4.19 (dd, 1H, J 8.0, 4.5 Hz, H1), 3.83 (s, 3H, OCH_3 -7), 3.81 (s, 3H, OCH_3 -5'), 3.83-3.70 (m, 2H, 2H3), 3.78 (s, 3H, OCH_3 -4'), 3.75 (s, 3H, OCH_3 -6), 3.65 (dq, 2H, J 14.5, 6.5, $OCHHCH_3$), 3.50 (dq, 2H, J 14.5, 6.5, $OCHHCH_3$), 3.22 (dd, 1H, J 13.5, 4.5 Hz, H7'), 3.07 (dd, 1H, J 12.5, 6.5 Hz, H1''), 2.89-2.84 (m, 2H, H7', H1''), 2.76 (d, 2H, J 5.0 Hz, 2xH1'''), 2.64-2.62 (m, 2H, 2xH4), 1.14 (t, 6H, J 6.5 Hz, 2 x OCH_2CH_3). ^{13}C NMR: δ 147.7 (C4'), 147.3 (C6), 147.1 (C5'), 146.9 (C7), 130.1 (C2'), 129.5 (C8a), 129.1 (C1'), 127.1 (C4a), 113.1 (CH-5), 112.8 (CH-3'), 111.4 (CH-6'), 109.3 (CH-8), 101.6 (CH-2'''), 62.1 (2 x OCH_2CH_3), 55.8 (CH-1), 55.9 (OCH_3 -7), 55.6 (OCH_3 -5', OCH_3 -4'), 55.5 (OCH_3 -6), 51.4 (CH_2 -1'''), 50.7 (CH_2 -3), 40.4 (CH_2 -1''), 38.6 (CH_2 -7'), 28.8 (CH_2 -4), 15.0 (2 x OCH_2CH_3). MS (ESI⁺): m/z 488.6 (MH^+ , 100%).

Attempted synthesis of (*RS*) 1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(2-oxoethylamino)methylphenyl]methyl-6,7-dimethoxyisoquinoline (32).

To a solution of **31** (71.3 mg, 0.146 mmol) in a mixture of CH₃OH (2 mL) and H₂O (1 mL) was added TsOH (75.3 mg, 0.438 mmol) to bring the pH to ~ 3. The reaction mixture was stirred at rt for 18 h. ESMS indicated only the unreacted **31**. The reaction was heated at 80 °C for 18 h, however only the precursor **31** was recovered and none of the desired aldehyde **32** was obtained.

(*RS*) 1,2,3,4-Tetrahydro-1[4',5'-dimethoxy-2'-(2,2-dimethoxyethylamino)methylphenyl]methyl-6,7-dimethoxyisoquinoline (33).

To a solution of the amine **31** (116 mg, 0.225 mmol) in CH₃OH (3 mL) was added 10% aqueous HCl (1 mL). The mixture was heated at reflux for 4 h. The solution was basified with K₂CO₃ (excess) to about pH ~6. The CH₃OH was evaporated and the residue was dissolved in CH₂Cl₂. The solution was washed with H₂O (3 x), brine and dried (K₂CO₃) to give **33** (37 mg, 41%) as a yellow oil. *R_f*: 0.1 (CH₃OH/EtOAc/NH₃ (5:5:0.1)). ¹H NMR: δ 6.86 (s, 1H, H3'), 6.75 (s, 1H, H5), 6.65 (s, 1H, H6'), 6.60 (s, 1H, H8), 4.51 (t, 1H, *J* 5.3 Hz, H2'''), 4.26 (dd, 1H, *J* 8.7, 3.9 Hz, H1), 3.86 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.81 (s, 3H, OCH₃-4'), 3.84-3.78 (m, 2H, 2xH3), 3.79 (s, 3H, OCH₃-6), 3.37 (s, 6H, 2 x OCH₃), 3.32-3.27 (m, 1H, H7'), 3.11 (dd, 1H, *J* 12.6, 4.2 Hz, H1''), 2.94-2.89 (m, 2H, H7', H1'''), 2.80 (dd, 2H, *J* 5.3, 2.1 Hz, 2xH1'''), 2.72-2.66 (m, 2H, 2xH4). ¹³C NMR: δ 148.4 (C4'), 148.3 (C6), 147.9 (C5'), 147.7 (C7), 133.4 (C2'), 129.4 (C8a), 128.6 (C1'), 127.6 (C4a), 114.7 (CH-5), 113.6 (CH-3'), 111.9 (CH-6'), 109.8 (CH-8), 103.8 (CH-2'''), 56.2 (OCH₃-7, OCH₃-5'), 56.1 (OCH₃-4', OCH₃-6), 54.6 (CH-1), 54.5 (2x OCH₃), 51.3 (CH₂-1'''), 53.9 (CH₂-3), 40.9 (CH₂-1''), 39.1 (CH₂-7'), 29.0 (CH₂-4). MS (ESI⁺): *m/z* 461.1 (MH⁺, 50%).

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(methylamino)methylphenyl]methyl-6,7-dimethoxyisoquinoline (36).

To a solution of the aldehyde **15** (136 mg, 0.290 mmol) and 33 % aqueous methylamine (0.05 mL) in CH₃CN (3 mL) was added NaCNBH₃ (24 mg, 0.377 mmol). The reaction was stirred at rt for 20 min before the pH was adjusted to ~ 6 using glacial acetic acid. The resulting solution was stirred for 18 h at rt. The CH₃CN was evaporated and the residue was dissolved in CH₂Cl₂. The solution was washed with H₂O (3x), sat. Na₂CO₃, brine and dried (MgSO₄) to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (5:5:0.1)) to afford **36** as a clear oil (100 mg, 71%). Compound **36** was a 95:5 mixture of rotamers. *R_f*: 0.35 (CH₃OH/EtOAc/NH₃ (5:5:0.1)). ¹H NMR of the major rotamer (500 MHz): δ 6.83 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.48 (s, 1H, H6'), 6.08 (s, 1H, H8), 5.53 (t, 1H, *J* 7.0 Hz, H1), 3.89 (dt, 1H, *J* 13.5, 4.5 Hz, H3), 3.82 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.72 (s, 3H, OCH₃-4'), 3.69 (dt, 1H, *J* 13.5, 3.5 Hz, H3), 3.54 (s, 3H, OCH₃-6), 3.50 (bs, 2H, 2xH1"), 3.11 (d, 2H, *J* 7.0 Hz, 2xH7'), 2.96-2.85 (m, 1H, H4), 2.80-2.72 (m, 1H, H4), 2.37 (s, 3H, NCH₃). ¹H NMR of the minor rotamer (in part): δ 6.77 (s, 1H, H3'), 6.53 (s, 1H, H5), 6.52 (s, 1H, H6'), 5.95 (s, 1H, H8), 5.09 (t, 1H, *J* 6.0 Hz, H1), 4.56 (dd, 1H, *J* 6.5 Hz, H3), 3.75 (s, 3H, OCH₃-5'). ¹³C NMR of the major rotamer: δ 156.0 (q, *J* 36.5 Hz, COCF₃), 148.1 (C4'), 147.7 (C6), 147.7 (C5'), 147.2 (C7), 130.4 (C2'), 127.7 (C8a), 126.5 (C1'), 124.8 (C4a), 116.4 (q, *J* 287.5 Hz, COCF₃), 114.0 (CH-5), 112.7 (CH-3'), 110.9 (CH-6'), 110.6 (CH-8), 58.9 (OCH₃-7), 55.8 (OCH₃-5'), 55.8 (OCH₃-4'), 55.6 (CH-1), 55.5 (OCH₃-6), 52.8 (CH₂-1"), 40.6 (CH₂-3), 37.8 (CH₂-7'), 36.0 (NCH₃), 28.4 (CH₂-4). MS (ESI⁺): *m/z* 483 (MH⁺, 30%). HRMS (ESI⁺): calcd for C₂₄H₃₀N₂O₅F₃, 483.2107 (MH⁺), found 483.2135.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(methylamino)ethyl phenyl]methyl-6,7-dimethoxyisoquinoline (37**).**

A mixture of aldehyde **16** (131 mg, 0.272 mmol) and 33 % aqueous methylamine (0.05 mL) in CH₃CN (3 mL) was added NaCNBH₃ (22 mg, 0.354 mmol). The mixture was treated as described above for the synthesis of **36** to give an oil. The oil was purified by column chromatography (CH₃OH/EtOAc/NH₃ (5:5:0.1)) to afford **37** as a yellow oil (82 mg, 62% yield). Compound **37** was a 95:5 mixture of rotamers. *R_f*: 0.25 (CH₃OH/EtOAc/NH₃ (5 : 5 : 0.1)). ¹H NMR of the major rotamer: δ 6.65 (s, 1H,

H3'), 6.58 (s, 1H, H5), 6.53 (s, 1H, H6'), 5.98 (s, 1H, H8), 5.48 (t, 1H, *J* 6.0 Hz, H1), 3.93 (dt, 1H, *J* 13.5, 5.0 Hz, H3), 3.82 (s, 6H, OCH₃-7, OCH₃-5'), 3.73 (s, 3H, OCH₃-4'), 3.69 (td, 1H, *J* 12.5, 3.0 Hz, H3), 3.52 (s, 3H, OCH₃-6), 3.08 (d, 2H, *J* 6.0 Hz, 2xH7'), 2.95-2.88 (m, 1H, H4), 2.81-2.76 (m, 1H, H4), 2.64 (t, 2H, *J* 6.5 Hz, 2xH2''), 2.63-2.58 (m, 1H, H1''), 2.55 (dd, 1H, *J* 13.5, 6.5 Hz, H1''), 2.37 (s, 3H, NCH₃). ¹H NMR of the minor rotamer (in part): δ 6.62 (s, 1H, H3'), 3.78 (s, 3H, OCH₃-4'), 3.45 (s, 3H, OCH₃-6). ¹³C NMR of the major rotamer: δ 156.0 (q, *J* 36.9 Hz, COCF₃), 148.5 (C4'), 147.2 (C6), 147.5 (C5'), 147.4 (C7), 131.2 (C2'), 127.5 (C4a), 126.0 (C1'), 125.1 (C8a), 114.3 (CH-5), 116.9 (q, *J* 287.5 Hz, COCF₃), 112.9 (CH-3'), 111.2 (CH-6'), 110.9 (CH-8), 56.2 (OCH₃-7), 556.1 (OCH₃-5'), 56.1 (OCH₃-4'), 55.9 (CH-1), 55.8 (OCH₃-6), 53.1 (CH₂-2''), 40.9 (CH₂-3), 38.2 (CH₂-7'), 36.3 (NCH₃), 32.4 (CH₂-1''), 28.7 (CH₂-4). MS (ESI⁺): *m/z* 497.1 (MH⁺, 100%). HRMS (ESI⁺): calcd for C₂₅H₃₂F₃N₂O₅, 497.2263 (MH⁺), found 497.2237.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4'5'-dimethoxy-2'-(*N*-(2-chloromethylcarbonyl)-*N*-methyl-aminomethyl)phenyl]methyl-6,7-dimethoxyisoquinoline (38).

To a solution of **36** (99 mg, 0.206 mmol) in dry CH₂Cl₂ (5 mL) was added triethylamine (42 mg, 0.412 mmol, 0.06 mL) at 0 °C followed by chloroacetyl chloride (30 mg, 0.268 mmol, 0.02 mL). The reaction was brought to RT and was stirred for 18 h. The CH₂Cl₂ layer was diluted and extracted with 10% aqueous NaOH, washed with H₂O (2x) and brine. The CH₂Cl₂ layer was dried (K₂CO₃) and evaporated to give an oil. The oil was purified by column chromatography (EtOAc) to give **38** (92 mg, 80% yield) as a clear oil. Compound **38** was a 95:5 mixture of rotamers. R_f 0.67 (EtOAc). ¹H NMR of the major rotamer: δ 6.63 (s, 2H, H3', H6'), 6.58 (s, 1H, H5), 6.25 (s, 1H, H8), 5.45 (t, *J* 7.3 Hz, H1), 4.48 (d, 1H, *J* 14.7 Hz, H1''), 4.26 (d, 1H, *J* 14.7 Hz, H1''), 4.01 (ABq, 2H, 6.6 Hz, 2xH2'''), 3.66 (dd, 1H, *J* 4.5, 1.8 Hz, H3), 3.81 (s, 6H, OCH₃-7, OCH₃-5'), 3.79 (s, 3H, OCH₃-4'), 3.78-3.74 (m, 1H, H3), 3.62 (s, 3H, OCH₃-6), 3.18 (dd, 1H, *J* 13.5, 8.1 Hz, H7'), 2.95 (dd, 1H, *J* 13.5, 6.9 Hz, H7'), 2.87-2.83 (m, 2H, 2xH4), 2.83 (s, 3H, NCH₃). ¹H NMR of the minor rotamer (in part): δ 6.50 (s, 1H, H5), 6.20 (s, 1H, H8). ¹³C NMR of the major rotamer: (signals for COCF₃ and COCF₃ were not observed), δ 166.5 (COCH₂Cl),

148.7 (C4'), 147.4 (C7), 148.1 (C5'), 147.5 (C6), 128.8 (C2'), 127.4 (C1'), 126.5 (C4a), 125.1 (C8a), 114.4 (CH-3'), 113.4 (CH-6'), 111.1 (CH-5), 110.9 (CH-8), 56.3 (OCH₃-7), 56.1 (OCH₃-5', OCH₃-4'), 56.0 (OCH₃-6), 55.4 (CH-1), 48.3 (CH₂-1''), 41.9 (CH₂-2'''), 40.8 (CH₂-3), 37.7 (CH₂-7'), 34.6 (NCH₃), 28.8 (CH₂-4). ¹³C NMR of the minor rotamer (in part): δ 114.9 (CH-3), 113.6 (CH-6'), 111.3 (CH-5), 50.6 (CH₂-1''), 42.7 (CH₂-2'''), 41.1 (CH₂-3), 38.0 (CH₂-7'), 28.5 (CH₂-4). MS (ESI⁺): *m/z* 581.0 (M(³⁵Cl)+Na⁺, 10%), 583.0 (M(³⁷Cl)+Na⁺, 4%). HRMS (ESI⁺): calcd for C₂₆H₃₀F₃N₂NaO₆³⁵Cl, 581.1642 (M(³⁵Cl)+Na⁺), found 581.1641.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(*N*-(2-chloromethyl carbonyl)-*N*-ethyl-aminomethyl)phenyl]methyl-6,7-dimethoxyisoquinoline (39).

To a solution of **38** (73 mg, 0.152 mmol) in dry CH₂Cl₂ (5 mL) was added triethylamine (31 mg, 0.304 mmol, 0.041 mL) at 0°C, followed by chloroacetyl chloride (22 mg, 0.198 mmol, 0.013 mL). The reaction mixture was brought to rt and stirred for 18 h. The mixture was worked up as described above in the synthesis of **38** to give an oil. The oil was purified by column chromatography (EtOAc) to give **39** (63 mg, 72%) as a clear oil. Compound **39** was a 95:5 mixture of rotamers. *R_f*: 0.60 (EtOAc). ¹H NMR of the major rotamer: δ 6.61 (s, 1H, H3'), 6.58 (s, 1H, H6'), 6.55 (s, 1H, H5), 6.13 (s, 1H, H8), 5.46 (dd, 1H, *J* 8.4, 6.3 Hz, H1), 4.01 (s, 2H, 2xH2'''), 3.90 (dt, 1H, *J* 5.4, 2.1 Hz, H3), 3.81 (s, 6H, OCH₃-7, OCH₃-5'), 3.82-3.78 (m, 1H, H3), 3.75 (s, 3H, OCH₃-4'), 3.57 (s, 3H, OCH₃-6), 3.45 (dt, 1H, *J* 9.6, 3.6 Hz, H2''), 3.29-3.19 (m, 2H, H2'', H7'), 3.06-2.99 (m, 1H, H7'), 2.97 (s, 3H, NCH₃), 2.89-2.84 (m, 2H, 2xH4), 2.61-2.53 (m, 2H, 2xH1''). ¹H NMR of the minor rotamer (in part): δ 6.59 (s, 1H, H3'), 6.40 (s, 1H, H5), 5.90 (s, 1H, H8), 5.36 (dd, 1H, *J* 9.3, 4.8 Hz, H1), 3.67 (s, 6H, OCH₃-7, OCH₃-5'), 3.63 (s, 3H, OCH₃-4'), 3.50 (s, 3H, OCH₃-6). ¹³C NMR of the major rotamer: (signals for C=O and C=O were not observed), δ 116.1 (C=OCH₂Cl), 148.1 (C4'), 147.9 (C7), 147.4 (C5'), 147.1 (C6), 129.8 (C2'), 127.6 (C1'), 126.3 (C4a), 124.8 (C8a), 114.0 (CH-3'), 112.8 (CH-6), 110.8 (CH-5), 110.6 (CH-8), 56.9 (OCH₃-7), 56.8 (OCH₃-5'), 55.8 (OCH₃-4'), 55.7 (OCH₃-6), 55.6 (CH-1), 50.4 (CH₂-2'''), 41.3 (CH₂-2''), 40.5 (CH₂-3), 37.8 (CH₂-7'), 36.3 (NCH₃),

29.7 (CH₂-1"), 28.4 (CH₂-4). ¹³C NMR of the minor rotamer (in part): δ 129.2 (C2'), 127.2 (C1'), 125.1 (C8a), 114.4 (CH-3), 112.6 (CH-6'), 110.9 (CH-5). MS (ESI⁺): *m/z* 573.0 (M(³⁵Cl)H⁺, 100%), 575.0 (M(³⁷Cl)H⁺, 40%). HRMS (ESI⁺): calcd for C₂₇H₃₃N₂O₆F₃³⁵Cl, 573.1979 (M(³⁵Cl)H⁺), found 573.1985.

(*RS*) 3-(1,2)-Benzena-5-(1,2)-isoquinolinacyclo-1-aza-7-oxo-heptaphane (40).

To a solution of **38** (92 mg, 0.165 mmol) in CH₃OH (4 mL) and H₂O (1 mL) was added K₂CO₃ (112 mg, 0.825 mmol), and the mixture was stirred at rt for 3 h. The CH₃OH was gently removed under pressure (without warming the water bath) to give an aqueous residue. To the mixture was added CH₂Cl₂ (10 mL), followed by the addition of triethylamine (0.3 mL). The reaction was stirred for 18 h at RT. The CH₂Cl₂ layer was washed with H₂O (3 x), brine and then dried (K₂CO₃). The solvent was removed to give an oil which was purified by column chromatography (EtOAc) to give **40** (41 mg, 57% yield) as a yellow oil. *R_f* 0.35 (EtOAc). ¹H NMR δ 6.69 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.41 (s, 1H, H6'), 5.96 (s, 1H, H8), 4.22 (bs, 1H, H1"), 3.99 (t, 1H, *J* 7.0 Hz, H1), 3.88 (s, 3H, OCH₃-7), 3.82 (s, 3H, OCH₃-5'), 3.79 (s, 3H, OCH₃-4'), 3.52 (s, 3H, OCH₃-6), 3.52 (bs, 6H, OCH₃-6, 2xH3", H1"), 3.38-3.32 (m, 1H, H7'), 3.09 (s, 3H, NCH₃), 2.86 (dt, 1H, *J* 10.5, 3.6 Hz, H3), 2.77 (dd, 1H, *J* 14.0, 3.0 Hz, H7'), 2.56 (ddd, 1H, *J* 14.0, 10.5, 2.5 Hz, H3), 2.27 (bs, 2H, 2xH4). ¹³C NMR δ 172.1 (C=O), 147.6 (C4'), 147.5 (C7), 147.4 (C5', C6), 130.0 (C2'), 129.8 (C1'), 129.2 (C4a), 129.0 (C8a), 115.0 (CH-8), 112.0 (CH-5), 111.0 (CH-6'), 110.4 (CH-3'), 64.0 (CH-1), 62.1 (CH₂-3"), 56.6 (OCH₃-7), 56.1 (OCH₃-5', OCH₃-4'), 55.8 (OCH₃-6), 54.5 (CH₂-1"), 49.7 (CH₂-3), 40.7 (CH₂-7'), 36.2 (NCH₃), 30.0 (CH₂-4). MS (ESI⁺): *m/z* 427.1 (MH⁺, 100%). HRMS (ESI⁺): calcd for C₂₄H₃₁N₂O₅, 427.2233 (MH⁺), found 427.2227.

(*RS*) 4-(1,2)-Benzena-6-(1,2)-isoquinolinacyclo-1-aza-8-oxo-octaphane (41).

The synthesis of the title compound **41** was carried out using the conditions described above for the synthesis of **40** starting with compound **39** (63 mg, 0.108 mmol), CH₃OH (3 mL), H₂O (1 mL) and K₂CO₃ (112 mg, 0.825 mmol). This was followed by intramolecular cyclisation using CH₂Cl₂ (10 mL) and triethylamine (0.3 mL) to

give an oil which was purified by column chromatography (EtOAc) to give **41** (31 mg, 46% yield) as a yellow oil. R_f 0.48 (EtOAc). ^1H NMR: δ 6.71 (s, 1H, H3'), 6.60 (s, 1H, H6'), 6.53 (s, 1H, H5), 6.36 (s, 1H, H8), 4.06-4.01 (m, 1H, H1), 3.90 (s, 3H, OCH_3 -7), 3.86 (s, 3H, OCH_3 -5'), 3.85 (s, 3H, OCH_3 -4'), 3.70 (s, 3H, OCH_3 -6), 3.47 (bs, 2H, 2xH4"), 3.29- 3.27 (m, 1H, H7'), 3.12-3.08 (m, 2H, 2xH2"), 3.05 (s, 3H, NCH_3), 3.00-2.93 (m, 1H, H3), 2.89-2.81 (m, 1H, H7'), 2.77-2.64 (m, 3H, 2xH1", H3), 2.22-2.16 (m, 2H, 2xH4). ^{13}C NMR: δ 171.4 (C=O), 148.5 (C4'), 147.9 (C7), 147.5 (C5'), 147.1 (C6), 131.7 (C2'), 131.6 (C1'), 128.6 (C4a), 127.9 (C8a), 114.7 (CH-8), 113.4 (CH-6'), 111.4 (CH-5), 110.6 (CH-3'), 65.1 (CH-1), 60.8 (CH_2 -4"), 56.4 (OCH_3 -7), 56.3 (OCH_3 -5'), 56.2 (OCH_3 -4'), 56.1 (OCH_3 -6), 53.0 (CH_2 -2"), 52.7 (CH_2 -3, CH_2 -7'), 35.3 (NCH_3), 33.8 (CH_2 -1", CH_2 -4). MS (ESI $^+$): m/z 441.1 (MH^+ , 100%). HRMS (ESI $^+$): calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_5$, 441.2389 (MH^+), found 441.2380.

(*RS*)-3-(1,2)-Benzena-5-(1,2)-isoquinolinacyclo-1-aza-heptaphane (42).

To a slurry of LiAlH_4 (38 mg, 1.02 mmol) in dry THF (1 mL) was added a solution of the amide **41** (21 mg, 0.048 mmol) in dry THF (1 mL) under a N_2 atmosphere at 0°C . The resulting mixture as brought to rt and stirred for 18 h. H_2O (0.2 mL), 1M aqueous NaOH (0.2 mL), H_2O (0.5 mL) were added subsequently and the reaction was stirred for 1 h. The solid was filtered and washed with EtOAc. The solution was dried (K_2CO_3) and evaporated to give **42** (16 mg, 81%) as a clear oil without the need for further purification. R_f 0.15 ($\text{CH}_3\text{OH}/\text{EtOAc}/\text{NH}_3$ (5:5:0.1)). ^1H NMR δ 6.84 (s, 1H, H3'), 6.64 (s, 1H, H6'), 6.58 (s, 2H, H5, H8), 4.50 (d, 1H, J 12.5 Hz, H1"), 4.22 (bs, 1H, H1), 3.89 (s, 3H, OCH_3 -7), 3.86 (s, 6H, OCH_3 -5', OCH_3 -4'), 3.83 (s, 3H, OCH_3 -6), 3.42 (d, 1H, J 12.5 Hz, H1"), 3.40 (dd, 1H, J 14.0, 7.0 Hz, H7'), 3.15-3.09 (m, 2H, 2xH3"), 2.81-2.72 (m, 3H, H3, 2xH2"), 2.68 (dd, 1H, J 14.0, 2.0 Hz, H7'), 2.59-2.51 (m, 3H, H3, 2xH4), 2.52 (s, 3H, NCH_3). ^{13}C NMR δ 147.6 (C4'), 147.4 (C7), 147.3 (C5'), 147.1 (C6), 134.0 (C2'), 132.2 (C1'), 131.5 (C4a), 127.5 (C8a), 114.4 (CH-3'), 113.8 (CH-6), 111.2 (CH-5), 110.7 (CH-8), 61.5 (CH-1), 58.1 (CH_2 -1"), 56.2 (OCH_3 -7), 56.0 (OCH_3 -5'), 56.0 (OCH_3 -4'), 55.8 (OCH_3 -6), 52.0 (CH_2 -2"), 51.9 (CH_2 -3), 48.0 (CH_2 -7'), 42.6 (NCH_3), 29.7 (CH_2 -3"), 27.1 (CH_2 -4). MS (ESI $^+$): m/z 413.2 (MH^+ , 100%).

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20. *CNS receptors tested*: μ (h) (MOP); A₁ (h); A_{2A} (h); A₃; α_1 ; α_2 ; β_1 ; AT₁ (h); BZD (central); B₂ (h); CCKA (h); D₁ (h); D_{2S} (h); ET_A (h); GABA (non selective); GAL2 (h); CXCR2 (h); CCR1; H₁ (h); H₂ (h); MC₄ (h); ML₁; M₁ (h); M₂ (h); M₃ (h); NK₂ (h); NK₃ (h); NT₁ (h); δ_2 (h); κ (KOP); ORL1 (h) (NOP); 5-HT_{1A} (h); 5-HT_{1B}; 5-HT_{2A} (h); 5-HT₃ (h); 5-HT_{5A} (h); 5-HT₆ (h); 5-HT₇ (h); sst (non-selective); VIP₁ (h); V_{1a} (h); Ca²⁺ channel; K⁺ channel; Na⁺ channel; SK⁺ Ca channel; Cl⁻ channel; NE transporter; DA transporter.
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GRAPHICAL ABSTRACT

Synthesis of 2'-Aminoalkyl-1-benzylisoquinoline derivatives and medium sized ring analogues with mu opiod receptor binding activities.

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